INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 99/02629

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D211/16 C07D295/18 A61K31/16 C07D295/22 C07C259/06
C07D211/60 C07D295/20 C07D217/06 C07D211/48 C07C321/16
C07C279/14 A61K31/445 A61K31/495 A61K31/47 A61P31/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 94 10990 A (GALLOWAY WILLIAM ALAN ;BRITISH BIO TECHNOLOGY (GB); CRIMMIN MICHAE) 26 May 1994 (1994-05-26) page 14, line 8	1-5
A	FOURNIE-ZALUSKI M -C ET AL: "NEW BIDENTASES AS FULL INHIBITORS OF ENKEPHALIN-DEGRADING ENZYMES: SYNTHESIS AND ANALGESIS PROPERTIES" JOURNAL OF MEDICINAL CHEMISTRY,US,AMERICAN CHEMICAL SOCIETY. WASHINGTON, vol. 28, no. 9, 1 January 1985 (1985-01-01), pages 1158-1169, XP002019770 ISSN: 0022-2623	

-/—

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 March 2000	15/03/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	De Jong, B

2

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 99/02629

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D211/58

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Y JIN ET AL: "Inhibition stereochemistry of hydroxamate inhibitors for thermolysin" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS,GB,OXFORD, vol. 8, no. 24, 1998, pages 3515-3518-3518, XP002106374 ISSN: 0960-894X	
E	WO 99 39704 A (BRITISH BIOTECH PHARM ;DAVIES STEPHEN JOHN (GB); HUNTER MICHAEL GE) 12 August 1999 (1999-08-12) cited in the application the whole document	1-5

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 March 2000	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	De Jong, B

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 99/02629

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 3,4
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 3,4 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 99/02629

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9410990 A	26-05-1994	AT 150300 T	15-04-1997
		AU 5430194 A	08-06-1994
		DE 69309094 D	24-04-1997
		DE 69309094 T	31-07-1997
		EP 0667770 A	23-08-1995
		ES 2101358 T	01-07-1997
		JP 8505605 T	18-06-1996
		US 5691382 A	25-11-1997
WO 9939704 A	12-08-1999	AU 2529299 A	23-08-1999

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 February 2001 (15.02.2001)

PCT

(10) International Publication Number
WO 01/10835 A1

(51) International Patent Classification[7]: C07D 211/16, 295/18, A61K 31/16, C07D 295/22, C07C 259/06, C07D 211/60, 295/20, 217/06, 211/48, C07C 321/16, 279/14, A61K 31/445, 31/495, 31/47, A61P 31/04, C07D 211/58

(21) International Application Number: PCT/GB99/02629

(22) International Filing Date: 10 August 1999 (10.08.1999)

10 FEB 02/30 mos.

(25) Filing Language: English

(26) Publication Language: English

(71) Applicant *(for all designated States except US)*: **BRITISH BIOTECH PHARMACEUTICALS LIMITED** [GB/GB]; Watlington Road, Cowley, Oxford OX4 5LY (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **HUNTER, Michael, George** [GB/GB]; British Biotech Pharmaceuticals Limited, Watlington Road, Cowley, Oxford OX4 5LY (GB). **BECKETT, Raymond, Paul** [GB/GB]; British Biotech Pharmaceuticals Limited, Watlington Road, Cowley, Oxford OX4 5LY (GB). **CLEMENTS, John, Martin** [GB/GB]; British Biotech Pharmaceuticals Limited, Watlington Road, Cowley, Oxford OX4 5LY (GB). **WHITTAKER, Mark** [GB/GB]; British Biotech Pharmaceuticals Limited, Watlington Road, Cowley, Oxford OX4 5LY (GB). **DAVIES, Stephen, John** [GB/GB]; British Biotech Pharmaceuticals Limited, Watlington Road, Cowley, Oxford OX4 5LY (GB). **PRATT, Lisa, Marie** [GB/GB]; British Biotech Pharmaceuticals Limited, Watlington Road, Cowley, Oxford OX4 5LY (GB). **SPAVOLD, Zoe, Marie** [GB/GB]; British Biotech Pharmaceuticals Limited, Watlington Road, Cowley, Oxford OX4 5LY (GB). **LAUNCHBURY, Steven** [GB/GB]; British Biotech Pharmaceuticals Limited, Watlington Road, Cowley, Oxford OX4 5LY (GB).

(74) Agent: **WALLS, Alan, J.**; British Biotech Pharmaceuticals Limited, Watlington Road, Cowley, Oxford OX4 5LY (GB).

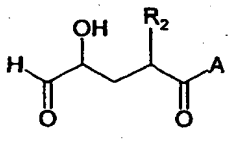
(81) Designated States *(national)*: AU, BR, CA, CN, CZ, GB, HU, IL, JP, KR, MX, NO, NZ, PL, RU, SG, SK, TR, UA, US, ZA.

(84) Designated States *(regional)*: European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published:
— *With international search report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: ANTIBACTERIAL AGENTS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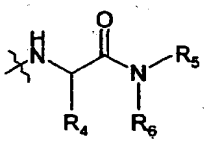
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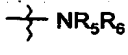

(IB)

(57) Abstract: Selected compounds of formula (I) are antibacterial agents: formula (I) wherein R_2 represents a substituted or unsubstituted C_1-C_6 alkyl, cycloalkyl (C_1-C_6 alkyl)- or aryl (C_1-C_6 alkyl)- group, and A represents a group of formula (IA), or (IB) wherein R_4 represents the side chain of a natural or non-natural alpha amino acid, and R_5 and R_6 are each independently hydrogen or C_1-C_6 alkyl, heterocyclic or aryl (C_1-C_6 alkyl)-, R_5 and R_6 when taken together with the nitrogen atom to which they are attached from an optionally substituted saturated heterocyclic ring of 3 to 8 atoms which ring is optionally fused to a carbocyclic or second heterocyclic ring.

WO 01/10835 A1

Antibacterial Agents

This invention relates to the use of N-formyl hydroxylamine derivatives as antibacterial agents, to a novel class of such compounds, and to pharmaceutical and veterinary compositions comprising such compounds.

Background to the Invention

In general, bacterial pathogens are classified as either Gram-positive or Gram-negative. Many antibacterial agents (including antibiotics) are specific against one or other Gram-class of pathogens. Antibacterial agents effective against both Gram-positive and Gram-negative pathogens are therefore generally regarded as having broad spectrum activity.

Many classes of antibacterial agents are known, including the penicillins and cephalosporins, tetracyclines, sulfonamides, monobactams, fluoroquinolones and quinolones, aminoglycosides, glycopeptides, macrolides, polymyxins, lincosamides, trimethoprim and chloramphenicol. The fundamental mechanisms of action of these antibacterial classes vary.

Bacterial resistance to many known antibacterials is a growing problem. Accordingly there is a continuing need in the art for alternative antibacterial agents, especially those which have mechanisms of action fundamentally different from the known classes.

Amongst the Gram-positive pathogens, such as Staphylococci, Streptococci, Mycobacteria and Enterococci, resistant strains have evolved/arisen which makes them particularly difficult to eradicate. Examples of such strains are methicillin resistant *Staphylococcus aureus* (MRSA), methicillin resistant coagulase negative Staphylococci (MRCNS), penicillin resistant *Streptococcus pneumoniae* and multiply resistant *Enterococcus faecium*.

Pathogenic bacteria are often resistant to the aminoglycoside, β-lactam (penicillins and cephalosporins), and chloramphenicol types of antibiotic. This resistance involves the enzymatic inactivation of the antibiotic by hydrolysis or by formation of inactive derivatives. The β-lactam (penicillin and cephalosporin) family of antibiotics are characterised by the presence of a β-lactam ring structure. Resistance to this family of antibiotics in clinical isolates is most commonly due to the production of a "penicillinase" (β-lactamase) enzyme by the resistant bacterium which hydrolyses the β-lactam ring thus eliminating its antibacterial activity.

Recently there has been an emergence of vancomycin-resistant strains of enterococci (Woodford N. 1998 Glycopeptide-resistant enterococci: a decade of experience. Journal of Medical Microbiology. 47(10):849-62). Vancomycin-resistant enterococci are particularly hazardous in that they are frequent causes of hospital based infections and are inherently resistant to most antibiotics. Vancomycin works by binding to the terminal D-Ala-D-Ala residues of the cell wall peptidioglycan precursor. The high-level resistance to vancomycin is known as VanA and is conferred by a genes located on a transposable element which alter the terminal residues to D-Ala-D-lac thus reducing the affinity for vancomycin.

In view of the rapid emergence of multidrug-resistant bacteria, the development of antibacterial agents with novel modes of action that are effective against the growing number of resistant bacteria, particularly the vancomycin resistant enterococci and β-lactam antibiotic-resistant bacteria, such as methicillin-resistant *Staphylococcus aureus*, is of utmost importance.

Brief Description of the Invention

This invention is based on the finding that certain N-formyl hydroxylamine derivatives have antibacterial activity, and makes available a new class of antibacterial agents. The inventors have found that the compounds with which this invention is concerned are antibacterial with respect to a range of Gram-positive and Gram-negative organisms.

Although it may be of interest to establish the mechanism of action of the compounds with which the invention is concerned, it is their ability to inhibit bacterial growth that makes them useful. However, it is presently believed that their antibacterial activity is due, at least in part, to intracellular inhibition of bacterial polypeptide deformylase (PDF; EC 3.5.1.31).

All ribosome-mediated synthesis of proteins starts with a methionine residue. In prokaryotes the methionyl moiety carried by the initiator tRNA is N-formylated prior to its incorporation into a polypeptide. Consequently, N-formylmethionine is always present at the N-terminus of a nascent bacterial polypeptide. However, most mature proteins do not retain the N-formyl group or the terminal methionine residue. Deformylation is required prior to methionine removal, since methionine aminopeptidase does not recognise peptides with an N-terminal formylmethionine residue (Solbiati et al., J. Mol. Biol. 290:607-614, 1999). Deformylation is, therefore, a crucial step in bacterial protein biosynthesis and the enzyme responsible, PDF, is essential for normal bacterial growth. Although the gene encoding PDF (*def*) is present in all pathogenic bacteria for which sequences are known (Meinnel et al., J. Mol. Biol, 266:939-49, 1997), it has no eukaryotic counterpart, making it an attractive target for antibacterial chemotherapy.

The isolation and characterisation of PDF has been facilitated by an understanding of the importance of the metal ion in the active site (Groche et al., Biophys. Biochem. Res. Commun., 246:324-6, 1998). The Fe^{2+} form is highly active *in vivo* but is unstable when isolated due to oxidative degradation (Rajagopalan et al., J. Biol. Chem. 273:22305-10, 1998). The Ni^{2+} form of the enzyme has specific activity comparable with the ferrous enzyme but is oxygen-insensitive (Ragusa et al., J. Mol. Biol. 1998, 280:515-23, 1998). The Zn^{2+} enzyme is also stable but is almost devoid of catalytic activity (Rajagopalan et al., J. Am. Chem. Soc. 119:12418-12419, 1997).

Several X-ray crystal structures and NMR structures of *E. coli* PDF, with or without bound inhibitors, have been published (Chan et al., Biochemistry 36:13904-9, 1997; Becker et al., Nature Struct. Biol. 5:1053-8, 1998; Becker et al., J. Biol. Chem. 273:11413-6, 1998; Hao et al., Biochemistry, 38:4712-9, 1999; Dardel et al., J. Mol. Biol. 280:501-13, 1998; O'Connell et al., J. Biomol. NMR, 13:311-24, 1999), indicating similarities in active site geometry to metalloproteinases such as thermolysin and the metzincins.

Recently the substrate specificity of PDF has been extensively studied (Ragusa et al., J. Mol. Biol. 289:1445-57, 1999; Hu et al., Biochemistry 38:643-50, 1999; Meinnel et al., Biochemistry, 38:4287-95, 1999). These authors conclude that an unbranched hydrophobic chain is preferred at P1', while a wide variety of P2' substituents are acceptable and an aromatic substituent may be advantageous at the P3' position. There have also been reports that small peptidic compounds containing an H-phosphonate (Hu et al., Bioorg. Med. Chem. Lett., 8:2479-82, 1998) or thiol (Meinnel et al., Biochemistry, 38:4287-95, 1999) metal binding group are micromolar inhibitors of PDF. Peptide aldehydes such as calpeptin (N-Cbz-Leu-norleucinal) have also been shown to inhibit PDF (Durand et al., Arch. Biochem. Biophys., 367:297-302, 1999). However, the identity of the metal binding group and its spacing from the rest of the molecule ("recognition fragment") has not been studied extensively. Furthermore, peptidic PDF inhibitors, which may be desirable from the point of view of bacterial cell wall permeability or oral bioavailability in the host species, have not been identified.

Related Prior Art

Certain N-formyl hydroxylamine derivatives have previously been claimed in the patent publications listed below, although very few examples of such compounds have been specifically made and described:

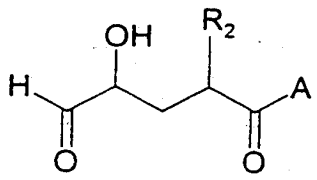
EP-B-0236872 (Roche)
WO 92/09563 (Glycomed)

WO 92/04735	(Syntex)
WO 95/19965	(Glycomed)
WO 95/22966	(Sanofi Winthrop)
WO 95/33709	(Roche)
WO 96/23791	(Syntex)
WO 96/16027	(Syntex/Agouron)
WO 97/03783	(British Biotech)
WO 97/18207	(DuPont Merck)
WO 98/38179	(GlaxoWellcome)
WO 98/47863	(Labs Jaques Logeais)

The pharmaceutical utility ascribed to the N-formyl hydroxylamine derivatives in those publications is the ability to inhibit matrix metalloproteinases (MMPs) and in some cases release of tumour necrosis factor (TNF), and hence the treatment of diseases or conditions mediated by those enzymes, such as cancer and rheumatoid arthritis. That prior art does not disclose or imply that N-formyl hydroxylamine derivatives have antibacterial activity.

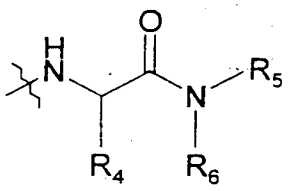
In addition to these, US-A-4,738,803 (Roques et al.) also discloses N-formyl hydroxylamine derivatives, however, these compounds are disclosed as enkephalinase inhibitors and are proposed for use as antidepressants and hypotensive agents. Also, WO 97/38705 (Bristol-Myers Squibb) discloses certain N-formyl hydroxylamine derivatives as enkephalinase and angiotensin converting enzyme inhibitors. This prior art does not disclose or imply that N-formyl hydroxylamine derivatives have antibacterial activity either.

Our copending International Patent Application No. PCT/GB99/0386 describes and claims, *inter alia*, the use of a compound of formula (I) or a pharmaceutically or veterinarily acceptable salt thereof in the preparation of an antibacterial composition:



(I)

wherein R_2 represents a substituted or unsubstituted C_1-C_6 alkyl, cycloalkyl(C_1-C_6 alkyl)-, or aryl(C_1-C_6 alkyl)- group, and A represents a group of formula (IA), or (IB):



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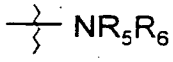


(IB)

wherein R_4 represents the side chain of a natural or non-natural alpha amino acid, and R_5 and R_6 are each independently hydrogen or C_1-C_6 alkyl, heterocyclic or aryl(C_1-C_6 alkyl)-, or R_5 and R_6 when taken together with the nitrogen atom to which they are attached form an optionally substituted saturated heterocyclic ring of 3 to 8 atoms which ring is optionally fused to a carbocyclic or second heterocyclic ring.

Detailed description of the invention

The present invention provides additional members of the class of compounds disclosed in PCT/GB99/00386, but which were not specifically identified or exemplified therein. As members of the class disclosed in PCT/GB99/00386, the present compounds are antibacterially active, and their mechanism of action is presently believed to be due at least in part to their ability to inhibit bacterial peptide deformylases.

Accordingly, the present invention provides a compound of formula (I) as defined above, selected from the group consisting of:

N-[3S-(4-benzylpiperidine-1-carbonyl)-2,2-dimethyl-propyl]-3-cyclopentyl-2R-[(formyl-hydroxy-amino)-methyl]-propionamide,

N-[2R-(4-benzyl-piperidine-1-carbonyl)-hexyl]-N-hydroxy-formamide,

N-hydroxy-N-[2R-(2-methyl-piperidine-1-carbonyl)-hexyl]-formamide,

N-hydroxy-N-[2R-(piperidine-1-carbonyl)-hexyl]-formamide,

N-hydroxy-N-[2R-(piperazine-1-carbonyl)-hexyl]-formamide,

2R-[(formyl-hydroxy-amino)-methyl]-hexanoic acid pyrrolidin-1-ylamide,

2R-[(formyl-hydroxy-amino)-methyl]-hexanoic acid methyl-(1-methyl-piperidin-4-yl)-amide,

N-[2R-(azepane-1-carbonyl)-hexyl]-N-hydroxy-formamide,

2R-[(formyl-hydroxy-amino)-methyl]-hexanoic acid (4-methyl-piperazin-1-yl)-amide,

2R-[(formyl-hydroxy-amino)-methy]-hexanoic acid diisopropylamide,

1-{2R-[(formyl-hydroxy-amino)-methyl]-hexanoyl}-piperidine-3-carboxylic acid ethyl ester,

4-{2R-[(formyl-hydroxy-amino)-methyl]-hexanoyl}-piperazine-1-carboxylic acid ethyl ester,

4-{2R-[(formyl-hydroxy-amino)-methyl]-hexanoyl}-1,1-dimethyl-piperazinium

iodide,

2R-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid [2,2-dimethyl-1S-(piperidine-1-carbonyl)-propyl]-amide,

2R-[(formyl-hydroxy-amino)-methyl]-hexanoic acid [1S-(3,4-dihydro-1*H*-isoquinoline-2-carbonyl)-2,2-dimethyl-propyl]-amide,

2R-[(formyl-hydroxy-amino)-methyl]-hexanoic acid [1S-(4-benzyl-4-hydroxy-piperidine-1-carbonyl)-2,2-dimethyl-propyl]-amide,

2R-[(formyl-hydroxy-amino)-methyl]-hexanoic acid [1S-(4-benzyl-piperazine-1-carbonyl)-2,2-dimethyl-propyl]-amide,

2R-[(formyl-hydroxy-amino)-methyl]-hexanoic acid (3-benzylsulfanyl-1S-dimethylcarbamoyl-propyl)-amide,

3S-{2R-[(formyl-hydroxy-amino)-methyl]-hexanoylamino}-*N*,*N*-dimethyl-succinamic acid benzyl ester,

4S-dimethylcarbamoyl-4-{2R-[(formyl-hydroxy-amino)-methyl]-hexanoyl-amino}-butyric acid benzyl ester,

(5S-dimethylcarbamoyl-5-{2R-[(formyl-hydroxy-amino)-methyl]-hexanoyl-amino}-pentyl)-dimethyl-ammonium chloride,

2R-[(formyl-hydroxy-amino)-methyl]-butyric acid (1-carbamoyl-2,2-dimethyl-propyl) amide,

2-[(formyl-hydroxy-amino)-methyl]-hexanoic acid (1-carbamoyl-2,2-dimethyl-propyl) amide,

2R-[formyl-hydroxy-amino)-methyl]-hexanoic acid (1-dimethyl-carbamoyl-4-guanidinobutyl)-amide,

2R-[2-(4-chlorophenyl)-3-(formyl-hydroxy-amino)-propionylamino]-2S-3,3,*N*,*N*-tetramethyl-butyramide,

2R-[(formyl-hydroxy-amino)-methyl]-hexanoic acid [2(3,4-dihydroxy-phenyl)-ethyl]-amide,

2R-[(formyl-hydroxy-amino)-methyl]-hexanoic acid [2(4-hydroxyphenyl)-ethyl]-amide,

and pharmacetically and veterinarily acceptable salts, hydrates and solvates thereof.

According to other aspects of the invention, there is provided (a) the use of a compound specifically named immediately above, or a pharmaceutically or veterinarily acceptable salt solvate or hydrate thereof, in the preparation of an antibacterial composition; (b) a method for the treatment of bacterial infections in humans and non-human mammals, which comprises administering to a subject suffering such infection an antibacterially effective dose of a compound specifically named immediately above, or a pharmaceutically or veterinarily acceptable salt solvate or hydrate thereof; (c) a method for the treatment of bacterial contamination by applying an antibacterially effective amount of a compound specifically named immediately above, or a pharmaceutically or veterinarily acceptable salt solvate or hydrate thereof, to the site of contamination; and (d) a pharmaceutical or veterinary composition comprising a compound specifically named immediately above, or a pharmaceutically or veterinarily acceptable salt solvate or hydrate thereof, together with a pharmaceutically or veterinaril acceptable carrier.

Of the compounds of the invention, the following are presently especially preferred

for their potency as antibacterial agents:

N-[3S-(4-benzylpiperidine-1-carbonyl)-2,2-dimethyl-propyl]-3-cyclopentyl-2R-[(formyl-hydroxy-amino)-methyl]-propionamide,

2R-[(formyl-hydroxy-amino)-methyl]-hexanoic acid methyl-(1-methyl-piperidin-4-yl)-amide,

2R-[(formyl-hydroxy-amino)-methyl]-hexanoic acid [1S-(4-benzyl-4-hydroxy-piperidine-1-carbonyl)-2,2-dimethyl-propyl]-amide,

2R-[(formyl-hydroxy-amino)-methyl]-hexanoic acid [1S-(4-benzyl-piperazine-1-carbonyl)-2,2-dimethyl-propyl]-amide,

2R-[(formyl-hydroxy-amino)-methyl]-hexanoic acid (3-benzylsulfanyl-1S-dimethylcarbamoyl-propyl)-amide, and

2-[(formyl-hydroxy-amino)-methyl]-hexanoic acid (1-carbamoyl-2,2-dimethyl-propyl) amide.

On the hypothesis that the compounds (I) act by inhibition of intracellular PDF, the most potent antibacterial effect may be achieved by using compounds which efficiently pass through the bacterial cell wall. Thus, compounds which are highly active as inhibitors of PDF in vitro and which penetrate bacterial cells are preferred for use in accordance with the invention. It is to be expected that the antibacterial potency of compounds which are potent inhibitors of the PDF enzyme in vitro, but are poorly cell penetrant, may be improved by their use in the form of a prodrug, ie a structurally modified analogue which is converted to the parent molecule of formula (I), for example by enzymic action, after it has passed through the bacterial cell wall.

Salts of the compounds of the invention include physiologically acceptable acid addition salts for example hydrochlorides, hydrobromides, sulphates, methane sulphonates, p-toluenesulphonates, phosphates, acetates, citrates, succinates, lactates, tartrates, fumarates and maleates. Salts may also be formed with bases, for example sodium, potassium, magnesium, and calcium salts.

Compositions with which the invention is concerned may be prepared for administration by any route consistent with the pharmacokinetic properties of the active ingredient(s).

Orally administrable compositions may be in the form of tablets, capsules, powders, granules, lozenges, liquid or gel preparations, such as oral, topical, or sterile parenteral solutions or suspensions. Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinyl-pyrrolidone; fillers for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricant, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants for example potato starch, or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, glucose syrup, gelatin hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

For topical application to the skin, the active ingredient(s) may be made up into a cream, lotion or ointment. Cream or ointment formulations which may be used for the drug are conventional formulations well known in the art, for example as described in standard textbooks of pharmaceutics such as the British Pharmacopoeia.

The active ingredient(s) may also be administered parenterally in a sterile medium. Depending on the vehicle and concentration used, the drug can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as a local anaesthetic, preservative and buffering agents can be dissolved in the vehicle. Intra-venous infusion is another route of administration for the compounds used in accordance with the invention.

Safe and effective dosages for different classes of patient and for different disease states will be determined by clinical trial as is required in the art. It will be understood that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

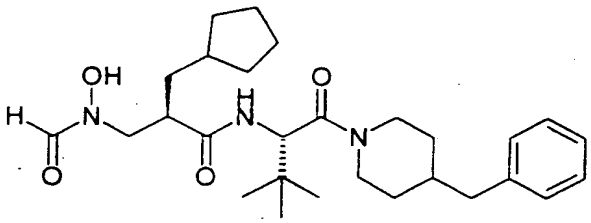
The following Examples describe the preparation of the compounds of the invention . In the Examples, ^{1}H and ^{13}C NMR spectra were recorded using a Bruker DPX 250 spectrometer at 250.1 and 62.9MHz, respectively. Mass spectra were obtained using a Perkin Elmer Sciex API 165 spectrometer using both positive and negative ionisation modes. Infra-red spectra were recorded on a Perkin Elmer PE 1600 FTIR spectrometer. The following abbreviations have been used throughout:

DIAD	Diisopropylazodicarboxylate
DIPEA	Diisopropylethylamine
DMF	N,N-Dimethylformamide

EDC	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
HOAt	1-Hydroxy-7-aza-benzotiazole
HOBt	1-Hydroxybenzotriazole
LRMS	Low resolution mass spectrometry
THF	Tetrahydrofuran

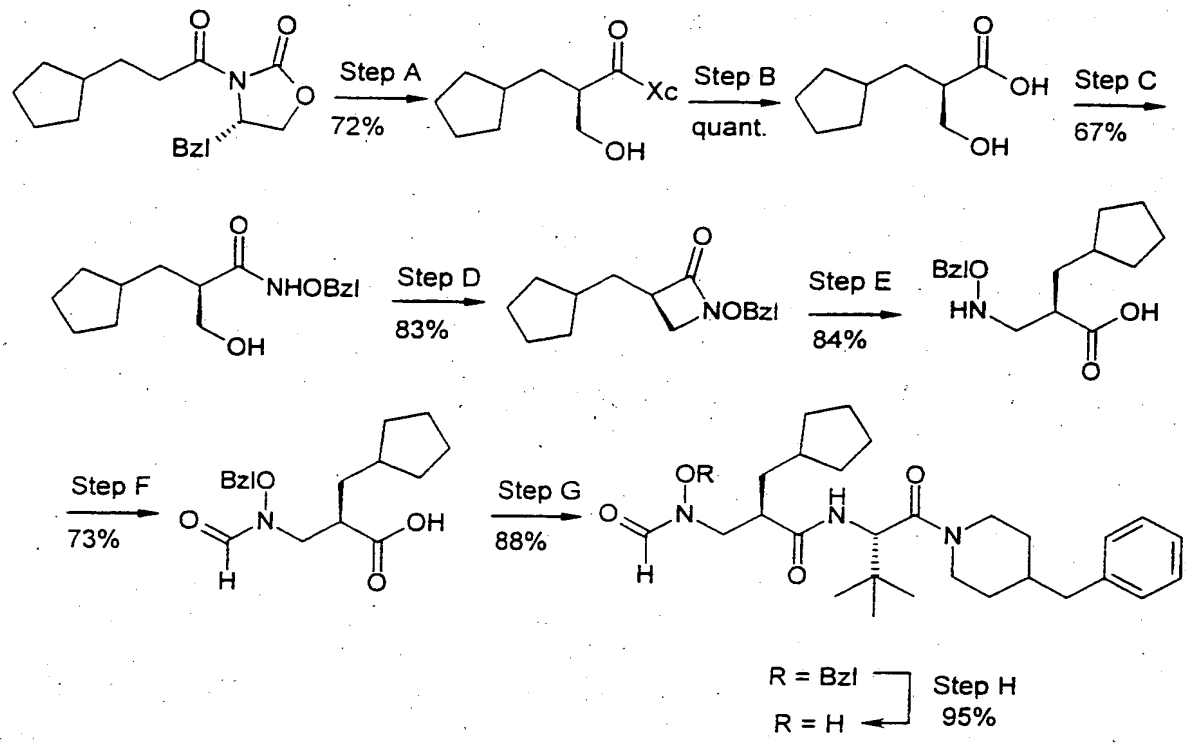
Example 1

N-[3S-(4-Benzylpiperidine-1-carbonyl)-2,2-dimethyl-propyl]-3-cyclopentyl-2R-[(formyl-hydroxy-amino)-methyl]-propionamide



The title compound was prepared as detailed below (see also Scheme 1)

Scheme 1



Reagents and Conditions: A: $TiCl_4$, trioxane, CH_2Cl_2; B: H_2O_2, LiOH; C: H_2NOBn, WSC, THF/H_2O; D: Ph_3P, DIAD, THF; E: LiOH, $THF/MeOH/H_2O$; F: formic acetic anhydride, NEt_3, THF; G: H-Tle-amide, EDCI, HOAt, DMF; H: Pd/C, H_2, MeOH.

Step A: 4S-Benzyl-3-[3-cyclopentyl-2R-hydroxymethyl-propionyl]-oxazolidin-2-one

To a stirred, cooled (0 °C) solution of 4S-benzyl-(3-cyclopentyl-propionyl)-oxazolidin-2-one (21 g, 69.8 mmol) in dichloromethane (350 ml) was added a solution of titanium tetrachloride (1M in dichloromethane, 73.25 ml, 73.2 mmol), dropwise. The resulting yellowish slurry was stirred for 10 minutes at 0 °C, and then DIPEA (13.37 ml, 76.7 ml) was added dropwise to furnish a dark-red solution. The stirring was maintained for 1 h at 0 °C, and then a solution of *s*-trioxane (7.53 g, 83.7 mmol), in dichloromethane (70 ml) was added dropwise followed by the addition of a solution of titanium tetrachloride (1M in dichloromethane, 73.25 ml, 73.2 mmol). The reaction mixture was then stirred

for 4 h at 0 °C. Saturated aqueous ammonium chloride (250 ml) was added to the reaction mixture and the aqueous layer was extracted with additional dichloromethane (2x300 ml). The combined organic layers were washed with water (150 ml) and with brine (80 ml), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo* to yield a yellow solid which on trituration with diethyl ether furnished a white solid (16.57 g, 72%). ^{1}H-NMR; $\delta(CDCl_3)$, 7.38-7.22 (5H, m), 4.70 (1H, m), 4.22-4.18 (2H, m), 3.99 (1H, m), 3.96-3.75 (2H, m), 3.31 (1H, dd, J = 13.4 & 3.3 Hz), 2.82 (1H, dd, J = 13.4 & 9.4 Hz), 2.24 (1H, dd, J = 8.3 & 4.5 Hz), 2.81-1.30 (4H, m) and 1.13 (1H, m); ^{13}C-NMR; $\delta(CDCl_3)$, 176.3, 153.6, 135.2, 129.5, 129.0, 127.4, 66.2, 64.2, 55.7, 44.8, 37.9, 37.8, 34.6, 33.0, 32.4 and 25.1.

Step B: 3-Cyclopentyl-2R-hydroxymethyl-propionic acid

To a stirred, cooled (0 °C) solution of 4S-Benzyl-3-[3-cyclopentyl-2R-hydroxymethyl-propionyl]-oxazolidin-2-one (16.05 g, 48.5 mmol) in THF-water (4:1, 250 ml) was added 27.5% aqueous hydrogen peroxide (24 ml, 194 mmol), followed by lithium hydroxide monohydrate (4.07 g, 97 mmol) in water (50 ml). After the reaction was complete (30 min), THF was removed *in vacuo*. The aqueous layer was extracted with dichloromethane (3x100 ml) and acidified to pH 2 with 4M hydrochloric acid. The aqueous layer was extracted with diethyl ether (2x150 ml). The combined organic layers were washed with brine (60 ml), dried over anhydrous magnesium sulfate and filtered. The solvent was removed *in vacuo* to afford a yellow oil which was further purified by column chromatography (25% ethyl acetate in hexanes to 100% ethyl acetate) to furnish the title compound as an oil (8.3 g, quant.). ^{1}H-NMR; δ ($CDCl_3$), 6.60-5.90 (1H, br s), 3.80-3.78 (2H, m), 2.67 (1H, m), 1.98-1.40 (9H, m) and 1.20-0.98 (2H, m). ^{13}C-NMR; $\delta(CDCl_3)$, 181.0, 63.2, 46.9, 37.8, 34.5, 32.7, 32.6, 25.1 and 25.1.

Step C: *N*-Benzyloxy-3-cyclopentyl-2R-hydroxym thyl-propionamide

To a stirred, cooled (0 °C) mixture of 3-cyclopentyl-2R-hydroxymethyl-propionic acid (1.1 g, 6.4 mmol) in THF-water (4:1, 30 ml), was added O-benzylhydroxylamine. The

pH of the resulting solution was adjusted to 4.5 by addition of 1M hydrochloric acid, and then EDC (1.84 g, 9.6 mmol) was added in one portion. The resulting solution was stirred for 2.5 h at room temperature while controlling pH at 4.5 by addition of 1M hydrochloric acid. After removal of the THF, the aqueous layer was extracted with ethyl acetate (3x40 ml) and the combined organic layers were washed with 10% citric acid (3x15 ml), 5% sodium hydrogen carbonate and dried over anhydrous magnesium sulfate. The solvent was removed *in vacuo* to afford the title compound as a colourless crystalline solid (1.18 g, 67%). This compound was then used without any further purification. ^{1}H-NMR; δ($CDCl_3$), 8.14 (1H, br s), 7.40-7.34 (5H, m), 4.94 (2H, br s), 3.76-3.66 (2H, m), 1.79-1.47 (11H, m) and 1.17-0.97 (2H, m). LRMS: +ve ion 278 [M+H], 555 [2M+H].

Step D: N-Benzyloxy-3R-cyclopentylmethyl-azetidin-2-one

To a stirred, cooled (0 °C) solution of *N*-Benzyloxy-3-cyclopentyl-2R-hydroxymethyl-propionamide (8.63 g, 31.1 mmol) and triphenylphosphine (9 g, 34.2 mmol) in dry THF (320 ml) was added DIAD (6.12 ml, 31.1 mmol), dropwise. The resulting solution was stirred at room temperature overnight. After removal of THF *in vacuo*, the residue was purified by column chromatography (hexanes:ethyl acetate, 5:1 to 3:1) to give the desired product as a white solid (6.7 g, 83%). ^{1}H-NMR; δ ($CDCl_3$), 7.76-7.39 (5H, m), 4.94 (2H, br s), 3.36 (1H, m), 2.96-2.80 (2H, m), 1.89-1.38 (9H, m) and 1.18-0.98 (2H, m). ^{13}C-NMR; δ ($CDCl_3$), 167.7, 129.6, 129.3, 129.0, 78.1, 52.5, 45.1, 39.1, 35.2, 33.1, 32.9, 25.5 and 25.3. LRMS: +ve ion 260 [M+H], 519 [2M+H].

Step E: 2R-(Benzyloxyamino-methyl)-3-cyclopentyl-propionic acid

To a stirred, cooled (0 °C) solution of *N*-Benzyloxy-3R-cyclopentylmethyl-azetidin-2-one (6.7 g, 25.8 mmol) in THF-methanol (3:1, 100 ml) was added lithium hydroxide monohydrate (1.3 g, 31.0 mmol) in water (25 ml). The reaction mixture was stirred and allowed to warm to room temperature overnight. The solvent was removed *in vacuo* and the aqueous layer was extracted with diethyl ether, then acidified to pH 2 by

addition of 4M hydrochloric acid. The aqueous layer was extracted with diethyl ether (3x40 ml), and the combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo* to give the title compound as white crystals (6.02 g, 84%). ^{1}H-NMR; δ ($CDCl_3$), 7.68-7.30 (5H, m), 4.78-4.68 (2H, m), 3.12-3.10 (2H, d, J = 6.9 Hz), 2.76 (1H, m), 1.91-1.39 (11H, m), 1.20-1.00 (2H, m). ^{13}C-NMR; δ ($CDCl_3$), 180.1, 137.7, 129.0, 128.9, 128.5, 78.0, 53.9, 42.9, 38.3, 36.6, 33.1, 33.0, 25.5. LRMS: -ve ion 276 [M-H], 553 [2M-H].

Step F: 2R-[(Benzyloxy-formyl-amino)-methyl]-3-cyclopentyl-propionic acid

To a stirred, cooled (0 °C) solution of 2R-(benzyloxyamino-methyl)-3-cyclopentyl-propionic acid (3.79 g, 13.7 mmol) in THF (20 ml) was added formic acetic anhydride (3.01 g, 34.2 mmol) and triethylamine (5.72 ml, 41.0 mmol). The reaction mixture was stirred for 1 h at 0 °C and 45 min at room temperature. The solvent was removed *in vacuo* and the mixture was purified by flash chromatography (hexanes: ethyl acetate, 1:1) to give the title compound as a yellow oil (3.04 g, 73%). LRMS: -ve ion 304 [M-H], -ve ion 609 [2M-H].

Step G: 2R-[(Benzyloxy-formyl-amino)-methyl]-*N*-[1S-(4-benzyl-piperidine-1-carbonyl)-2,2-dimethyl-propyl]-3-cyclopentyl-propionamide

To a stirred, cooled (0 °C) solution of 2R-[(Benzyloxy-formyl-amino)-methyl] -3-cyclopentyl-propionic acid (396 mg, 1.3 mmol) and 2S-Amino-1-(4-benzyl-piperidin-1-yl)-3,3-dimethyl-butan-1-one (see below) in DMF (5 ml), were added EDC (274 mg, 1.43 mmol) and HOAt (8.8 mg, 0.065 mmol). The reaction mixture was stirred overnight at room temperature. DMF was removed *in vacuo* to furnish a yellow oil, which was dissolved in ethyl acetate. The organic layer was then washed with 1M hydrochloric acid (2x5 ml) and water (5 ml). The aqueous layer was re- extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and

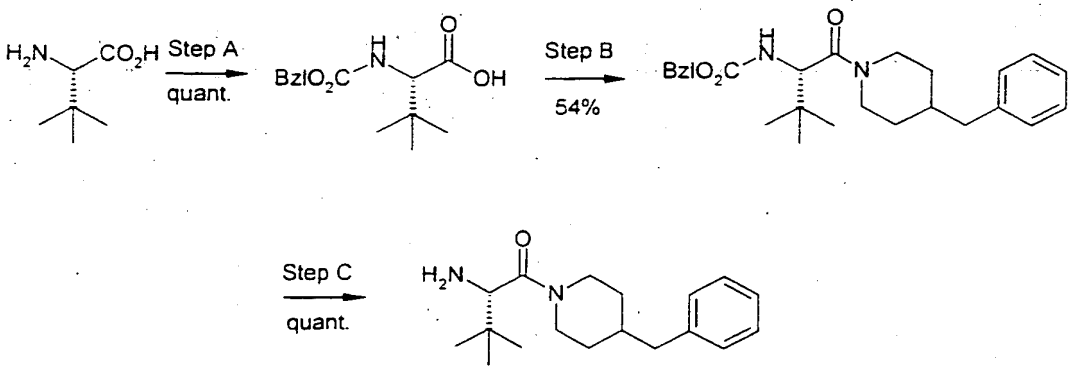
the solvent was removed *in vacuo* to furnish a white foam (660 mg, 88%) which was used in the next step without any purification.

Step H: *N*-[1*S*-(4-benzylpiperidine-1-carbonyl)-2,2-dimethyl-propyl]-3-cyclopentyl-2R-[(formyl-hydroxy-amino)-methyl]-propionamide

To a stirred solution of the 2R-[(benzyloxy-formyl-amino)-methyl]-*N*-[1S-(4-benzylpiperidine-1-carbonyl)-2,2-dimethyl-propyl]-3-cyclopentyl-propionamide (655 mg, 1.14 mmol) in Methanol (8 ml) under an argon atmosphere was added Pd/C (70 mg). Hydrogen gas was bubbled through the suspension for 30 min. The reaction mixture was then filtered through celite and the solvent was removed *in vacuo* to afford a pale pink solid (522 mg, 95%). ^{1}H-NMR; δ ($CDCl_3$, rotamers), 8.40 (0.4H, m), 7.83 (0.6H, m), 7.34-7.09 (5H, m), 6.55 (1H, m), 4.90 (1H, m), 4.57 (1H, m), 4.11-3.99 (1.5H, m), 3.85-3.77 (0.8H, m), 3.63-3.59 (0.7H, m), 3.51-3.47 (0.6H, m), 3.08-2.95 (1.2H, m), 2.88-2.62 (1.2H, m), 2.57-2.49 (3H, m), 1.89-0.90 (25H, m). LRMS: +ve ion 508 [M+Na], -ve ion 484 [M-H].

Preparation of 2S-Amino-1-(4-benzyl-piperidin-1-yl)-3,3-dimethyl-butan- 1-one (see Scheme 2)

Scheme 2



Reagents and conditions: A. NEt_3, N-(benzyloxycarbonyloxy)-succinimide, MeOH; B. EDCI, HOAt, DMF; C. cyclohexene, Pd/C, EtOH

Step A: 2S-Benzyloxycarbonylamino-3,3-dimethyl-butyric acid

To a suspension of L-*tert*-leucine (11.88 g, 90.7 mmol) in methanol (200 ml) were added triethylamine (26.56 ml, 190 mmol) and *N*-(benzyloxycarbonyl- oxy)-succinimide (24.88 g, 99.8 mmol). The reaction mixture was stirred at room temperature for 14 h. Methanol was removed *in vacuo* to afford a viscous pale yellow oil, which was dissolved in ethyl acetate (100 ml). The organic layer was washed with 1M hydrochloric acid (15 ml) and brine, dried over anhydrous magnesium sulfate and filtered. The solvent was removed *in vacuo* to furnish the title compound as an oil (24 g, quant.). ^{1}H-NMR; $\delta(CDCl_3)$, 7.43-7.36 (5H, m), 5.36 (1H, d, J = 9.4 Hz), 5.12 (2H, br s), 4.20 (1H, d, J = 9.6 Hz) and 1.02 (9H, s). LRMS: +ve ion 266 [M+H], -ve ion 264 [M-H], 529 [2M-H].

Step B: 2*S*-[1-(4-Benzyl-piperidine-1-carbonyl)-2,2-dimethyl-propyl-carbamic acid benzyl ester

To a solution of 2S-Benzyloxycarbonylamino-3,3-dimethyl-butyric acid (923 mg, 3.48 mmol) and 4-benzyl piperidine (735µl, 4.18 mmol) in DMF (16 ml) were added EDC (734 mg, 3.83 mmol) and HOAt (10 mg, 0.07 mmol). The reaction mixture was stirred for 14 h at room temperature. DMF was removed *in vacuo* and the crude residue was dissolved in ethyl acetate. The organic layer was washed with 1M hydrochloric acid (2x10 ml), water (10 ml), brine (10 ml), dried over anhydrous magnesium sulfate and filtered. Removal of the solvent *in vacuo* and purification by column chromatography (hexanes:ethyl acetate, 5:1) provided the desired amide (784 mg, 54%). ^{1}H-NMR; $\delta(CDCl_3)$, 7.36-7.14 (10H, m), 5.65 (1H, m), 5.17-5.05 (2H, m), 4.70-4.49 (2H, m), 2.96 (1H, m), 2.57-2.47 (2H, m), 1.90-1.59 (2H, m) and 1.38-0.87 (14H, m). LRMS: +ve ion 423 [M+H].

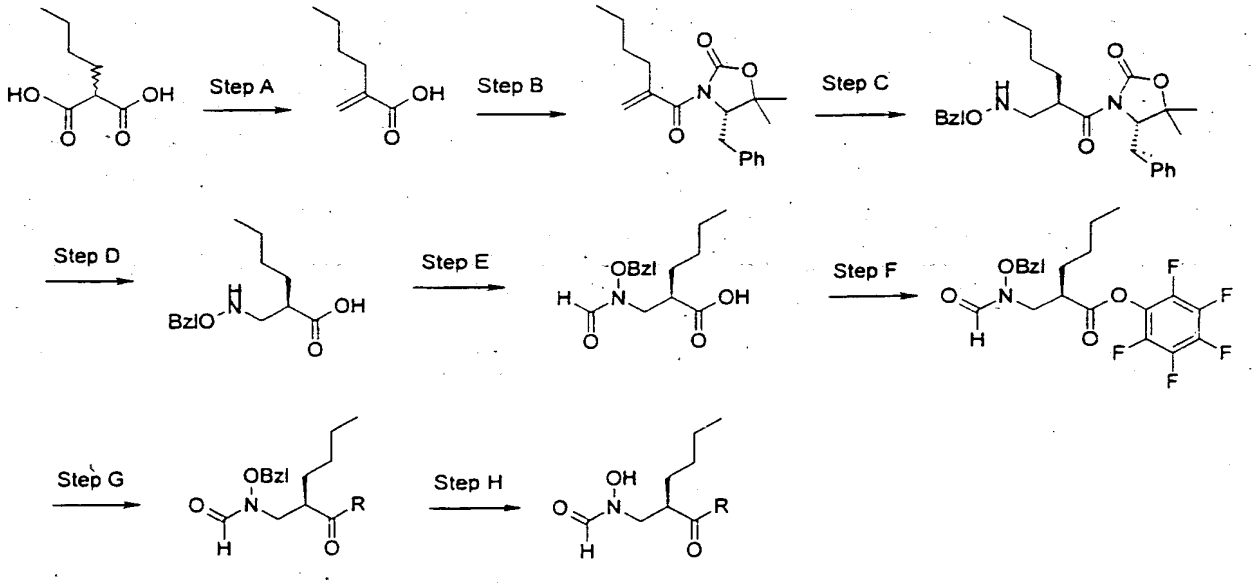
St p C: 2S-Amino-1-(4-benzyl-piperidin-1-yl)-3,3-dim thyl-butan-1-on

To a stirred solution of 2*S*-[1-(4-Benzyl-piperidine-1-carbonyl)-2,2-dimethyl-propyl-carbamic acid benzyl ester (784 mg, 1.86 mmol) in ethanol (4 ml) was added 10% palladium on charcoal (70 mg) and cyclohexene (380 µl, 3.71 mmol). The suspension was warmed to 75 °C for 1.5 h. The reaction mixture was filtered through celite and the solvent was removed *in vacuo* to afford quantitatively the title compound as a viscous oil. ^{1}H-NMR; δ($CDCl_3$), 7.32-7.12 (5H, m), 4.69 (1H, m), 4.01 (1H, m), 3.53 (1H, m), 2.86 (1H, m), 2.63-2.45 (3H, m), 1.80-1.63 (3H, m), 1.30-1.08 (3H, m), 0.99 (4.5H, m) and 0.94 (4.5H, m). LRMS: +ve ion 289 [M+H].

Examples 2-12

The compounds of Examples 2-12 (Table 1) were prepared in array format using the generic procedure outlined below (see also Scheme 3).

Scheme 3



Reagents and conditions: A. piperidine, HCHO, EtOH, 80°C, o/n; B. ^{t}BuCOCl, Et_3N then 3-lithio-4-benzyl-5,5-dimethyl-oxazolidin-2-one; C. H_2NOBzl, room temp., o/n then pTsOH, EtOAc; D. LiOH, aq THF, 0°C; E. formic acetic anhydride, Et_3N, THF; F. PfpOH, EDC, HOBt, THF; G. Amine; H. cyclohexene, Pd/C, EtOH.

Analytical HPLC was performed on a Beckman System Gold, using Waters Nova Pak C18 column (150 mm, 3.9 mm) with 20 to 90 % solvent B gradient (1 ml/min) as the mobile phase. [Solvent A: 0.05% TFA in 10% water 90% methanol; Solvent B: 0.05% TFA in 10% methanol 90%], detection wavelength at 230 nm. Preparative HPLC was performed on a Gilson autoprep instrument using a C18 Waters delta prep-pak cartridge (15µm, 300 A, 25 mm, 10 mm) with 20 to 90 % solvent B gradient (6 ml/min) as the mobile phase. [Solvent A water; Solvent B: methanol], UV detection was at 230 nm.

Step A: 2-Butyl acrylic acid

To a solution of n-butylmalonic acid (17.2 g, 107 mmol) in ethanol (200 ml) was added piperidine (12.76 ml, 129 mmol) and 37% aq. formaldehyde (40.3 ml, 538 mmol). The solution was heated to 80 °C during which time a precipitate appeared and gradually redissolved over 1 hour. The reaction mixture was stirred at 80 °C overnight then cooled to room temperature. The solvents were removed under reduced pressure and the residue was dissolved in ethyl acetate (200 ml), washed successively with 1 M hydrochloric acid and brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated to give the title compound as a clear oil (13.37 g, 97%). ^{1}H-NMR; δ ($CDCl_3$), 6.29 (1H, s), 5.65 (1H, s), 2.34-2.28 (2H, m), 1.54-1.26 (4H, m), 0.94 (3H, t, J = 7.1 Hz).

Step B: 4S-Benzyl-3-(2-butyl-acryloyl)-5,5-dimethyl-oxazolidin-2-one

2-Butyl acrylic acid (21.5 g, 168 mmol) was dissolved in dry THF (500 ml) and cooled to -78 °C under a blanket of argon. Triethylamine (30 ml, 218 mmol) and pivaloyl chloride (21 ml, 168 mmol) were added at such a rate that the temperature remained

below -60 °C. The mixture was stirred at -78 °C for 30 minutes, warmed to room temperature for 2 hours and finally cooled back to -78 °C.

In a separate flask, 4S-benzyl-5,5-dimethyl-oxazolidin-2-one was dissoved in dry THF (500ml) and cooled to -78 °C under a blanket of argon. n-Butyllithium (2.4 M solution in hexanes, 83 ml, 200 mmol) was added slowly and the mixture was stirred for 30 minutes at room temperature. The resulting anion was tranferred *via* a cannula into the original reaction vessel. The mixture was allowed to warm to room temperature and was stirred overnight at room temperature. The reaction was quenched with 1 M potassium hydrogen carbonate (200 ml) and the solvents were removed under reduced pressure. The residue was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure to give an orange oil. TLC analysis revealed the presence of unreacted chiral auxiliary in addition to the required product. A portion of the material (30 g) was dissolved in dichloromethane and flushed through a silica pad to give pure title compound as a yellow oil (25.3 g). ^{1}H-NMR; δ ($CDCl_3$), 7.31-7.19 (5H, m), 5.41 (2H,s), 4.51 (1H, dd, J = 9.7 & 4.2 Hz), 3.32 (1H, dd, J = 14.2 & 4.2 Hz), 2.82 (1H, dd, J = 14.2 & 9.7 Hz), 2.40-2.34 (2H, m), 1.48-1.32 (4H, m), 1.43 (3H, s), 1.27 (3H, s), 0.91 (3H, t, J = 7.1 Hz). Some chiral auxiliary was recovered by flushing the silica pad with methanol.

Step C: 4S-Benzyl-3-[2-(benzyloxyamino-methyl)-hexanoyl]-5,5-dimethyl-oxazolidin-2-one (p-toluenesulfonic acid salt)

4S-Benzyl-3-(2-butyl-acryloyl)-5,5-dimethyl-oxazolidin-2-one (19.8 g, 62.8 mmol) was mixed with O-benzylhydroxylamine (15.4 g, 126 mmol) and stirred overnight at room temperature. The mixture was dissolved in ethyl acetate and the solution was washed with 1 M hydrochloric acid, 1 M sodium carbonate and brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford a pale yellow oil (25.3 g) which was shown by NMR and HPLC analysis to contain 4S-benzyl-3-[2-(benzyloxyamino-methyl)-hexanoyl]-5,5-dimethyl-oxazolidin-2-

one (ca. 82% d.e.) along with a trace of starting material. The product was combined with another batch (26.9g, 76% d.e.) and dissolved in ethyl acetate (200 ml). p-Toluenesulfonic acid (22.7 g, 119 mmol) was added and the mixture was cooled to 0 °C. The title compound was obtained as a white crystalline solid by seeding and scratching. Yield: 25.2g, (34%, single diastereoisomer). A second crop (14.7 g, 20%, single diastereoisomer) was also obtained. ^{1}H-NMR;δ ($CDCl_3$), 7.89 (2H, d, J = 8.2 Hz), 7.37-7.12 (10H, m), 7.02 (2H, d, J = 6.9 Hz), 5.28-5.19 (2H, m), 4.55 (1H, m), 4.23 (1H, m), 3.93 (1H, m), 3.58 (1H, m), 2.58 (1H, m), 2.35 (3H, s), 1.67-1.51 (2H, m), 1.29-1.16 (4H, m), 1.25 (3H, s), 1.11 (3H, s), 0.80-0.75 (3H, m).

Step D: 2R-(Benzyloxyamino-methyl)-hexanoic acid

4S-Benzyl-3-[2R-(benzyloxyamino-methyl)-hexanoyl]-5,5-dimethyl-oxazolidin-2-one p-toluenesulfonic acid salt (25.2 g, 40.2 mmol) was partitioned between ethyl acetate and 1 M sodium carbonate. The organic phase was dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure. The residual oil was dissolved in THF (150 ml) and water (50 ml), cooled to 0 °C and treated with lithium hydroxide (1.86 g, 44.2 mmol). The solution was stirred for 30 minutes at 0 °C, then overnight at room temperature. The reaction was acidified to pH4 with 1 M citric acid and the solvents were removed. The residue was partitioned between dichloromethane and 1 M sodium carbonate. The basic aqueous layer was acidified to pH4 with 1M citric acid and extracted three times with ethyl acetate. The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated to provide the title compound as a colourless oil (7.4 g, 73%). ^{1}H-NMR;δ ($CDCl_3$), 8.42 (2H, br s), 7.34-7.25 (5H, m), 4.76-4.66 (2H, m), 3.20-3.01 (2H, m), 2.73 (1H, m), 1.70-1.44 (2H, m), 1.34-1.22 (4H, m) and 0.92-0.86 (3H, m).

Step E: 2R-[(B nzyloxy-formylamino)-methyl)]-hexanoic acid

To a solution of 2R-(Benzyloxyamino-methyl)-hexanoic acid (30.6 g, 0.12 mol) in dry THF (300 ml) was added formic acetic anhydride (26.8 ml, 0.31 mol) at 0 °C. Triethylamine (18.5 ml, 0.13 mol) was added and the reaction was stirred for 1 h at 0 °C and 60 h at room temperature. The solvent was removed *in vacuo* to yield the title compound as a yellow oil (33.6 g, 99%) which was used in Step F without further purification. ^{1}H-NMR; ($CDCl_3$, rotamers), 8.20-8.08 (0.7H, br s), 8.07-7.92 (0.3H, br s), 7.50-7.25 (5H, br m), 5.07-4.70 (2H, br m), 3.95-3.52 (2H, br m), 2.90-2.66 (1H, br s), 1.72-1.20 (6H, br m), 1.00-0.78 (3H, br s). LRMS: +ve ion 280 [M+1].

Step F: 2R-[(Benzyloxy-formyl-amino)-methyl]-hexanoic acid pentafluoro-phenyl ester

To a solution of 2R-[(Benzyloxy-formylamino)-methyl)]-hexanoic acid (7.8 g, 19.9 mmol) in dry THF (500 ml) was added pentafluorophenol (44.3 g, 0.24 mol), EDC (27.7 g, 0.14 mol) and HOBt (16.2 g, 0.12 mol). The reaction was stirred overnight at room temperature. The solvent was removed *in vacuo* and the residue was dissolved in ethyl acetate, washed successively with 1 M sodium carbonate (3 x 500 ml) and water (1 x 500 ml), dried over anhydrous magnesium sulfate and filtered. The solvent was removed *in vacuo* to yield a yellow oil (60 g) that was purified by flash chromatography (5:1, hexane:ethyl acetate → 1:2 hexane:ethyl acetate) to yield a clear oil (42.0 g, 79%). ^{1}H-NMR; δ($CDCl_3$, rotamers), 8.20-8.09 (0.7H, br s), 8.09-7.92 (0.3H, br s), 7.60-7.21 (5H, br m), 5.00-4.70 (2H, br m), 4.04-3.72 (2H, br m), 3.18-3.00 (1H, br s), 1.85-1.57 (2H, br m), 1.50-1.26 (4H, br m), 1.00-0.82 (3H, br m); LRMS: 466 [M+H].

Step G: Generic experimental procedure for the synthesis of an array of amides

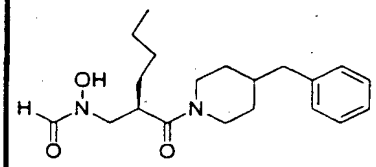
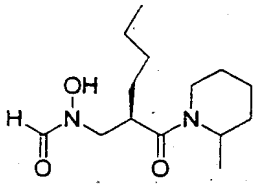
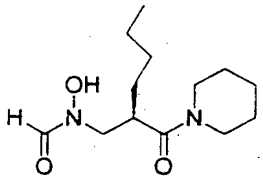
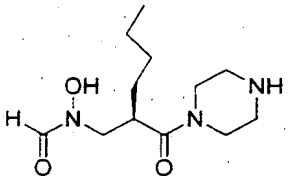
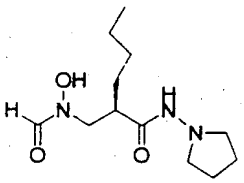
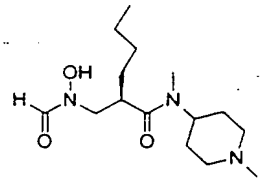
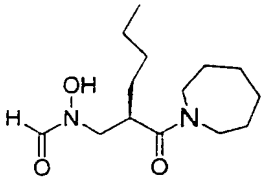
The coupling of amines to 2R-[(Benzyloxy-formyl-amino)-methyl]-hexanoic acid pentafluorophenyl ester was carried out on a Zymate XPII laboratory robot. To solutions of the pentafluorophenol ester (55.8 mg, 0.12 mmol) in dichloromethane (2

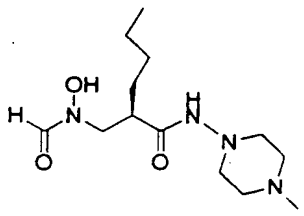
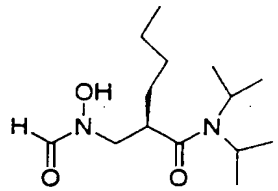
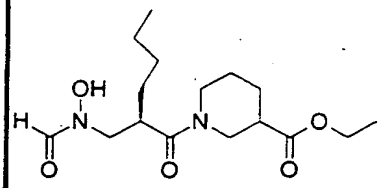
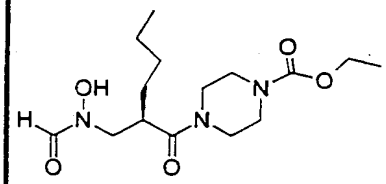
ml) were added individual amines (0.25 mmol) and the reaction mixtures were stirred at RT for 60 h. Purification was effected by removing excess amine and pentafluorophenol using scavenger resins. The pentafluorophenol was removed using a three fold excess (0.36 mmol) of A-26 carbonate resin (3.5 mmol loading). The resin was added to the reaction mixtures and agitated for 24 h, after which time it was filtered off. The excess amines were removed using a three-fold excess (0.36 mmol) of methylisocyanate polystyrene resin (1.2 mmol loading). The resin was added to the reaction mixtures and agitated for 4 h, after which time it was filtered off. The solvent was removed *in vacuo* using a Savant Speed Vac Plus to yield the coupled products. Yields were not calculated and the purity and integrity of each compound was verified using HPLC and LRMS.

Step H: Generic transfer hydrogenation procedure

Products from Step G were individually taken up in an ethanol (2.7ml) and cyclohexene (0.3 ml), 20% palladium on charcoal was added and the reactions stirred at 80 °C for 24 h. The Pd/C was filtered off and the solvent was removed *in vacuo* using a Savant Speed Vac Plus to yield the title compounds (examples **2-12**, Table 1). Yields were not calculated and the purity and integrity of each compound were verified using HPLC and LRMS

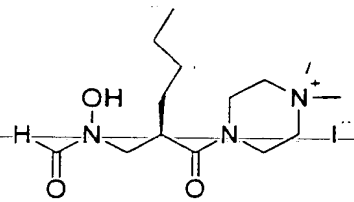
Table 1

Example	Structure	Mass Spectral Data	HPLC	Purification
2		347 (M+1, 100)	RT 18.5 min 100%	Resins
3		271 (M+1, 100), 293 (M+Na, 50)	RT 19.4 min 100%	Resins
4		257 (M+1, 50)	RT 24.4 min 100%	Resins
5		258 (M+1, 100)	RT 3.1 min and 3.5 min	Resins, Prep HPLC
6		258 (M+1, 100)	RT 4.0 min	Resins, Prep HPLC
7		300 (M+1, 100)	RT 4.2 min and 4.7 min (TFA salt)	Resins, Prep HPLC
8		271 (M+1, 100)	RT 18.5 min	Resins

9		287 (M+1, 100)	RT 3.0 min and 3.4 min	Resins, Prep HPLC
10		295 (M+1, 100)	Only prep RT	Prep HPLC
11		351 (M+Na, 100)	RT 7.6 min (grad 220nm)	Ion exchange Prep HPLC
12		330 (M+1, 100), 351 (M+Na, 50)	RT 16.8 min 100%	Resins

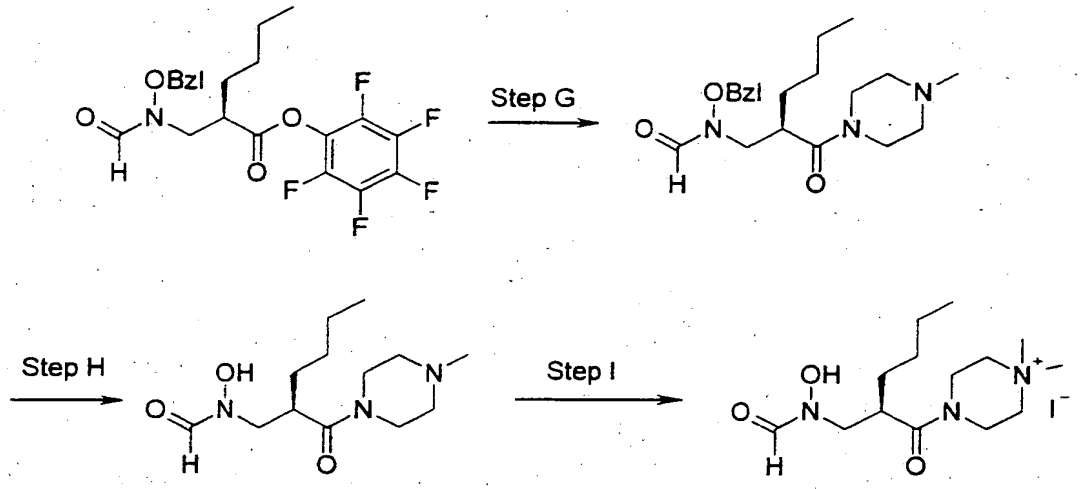
Example 13

2R,4-{2-[(Formyl-hydroxy-amino)-methyl]-hexanoyl}-1,1-dimethyl-piperazinium iodide



The title compound was prepared using the same procedure as for Examples 2 to12, except for the final methylation (see Scheme 4)

Scheme 4



Reagents and conditions: G. *N*-methylpiperazine; H. H_2, Pd/C, EtOH; I. MeI, dry THF.

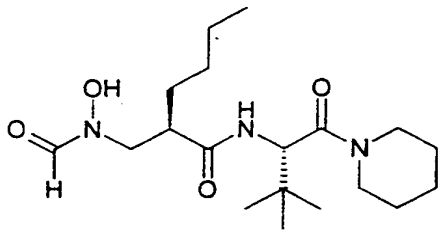
Step I: 2R,4-{2-[(Formyl-hydroxy-amino)-methyl]-hexanoyl}-1,1-dimethyl-piperazinium iodide

To a solution of N-hydroxy-N-[2R-(4-methyl-piperazine-1-carbonyl)-hexyl]-formamide (46 mg, 0.17 mmol) in anhydrous THF (5 ml) was added methyl iodide (22 µl, 0.34 mmol) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and at room temperature for 18 h. The solvent was removed *in vacuo* to yield the title compound as a white hygroscopic solid (68 mg, 97%). ^{1}H-NMR; CD_3OD, rotamers), 8.31 (0.7H, s), 7.88 (0.3H, s), 4.44-3.20 (17H, m), 1.75-1.20 (6H, m), 1.00-0.87 (3H, t, J = 6.6 Hz). LRMS: +ve ion 286 [M].

The compounds of Examples 14-17 were prepared from 2R-[(benzyloxy-formyl-amino)-methyl]-hexyl pentafluorophenyl ester (Example 2) and the appropriate L-tert-leucine derivatives by analogy with the method described in Example 2.

Example 14

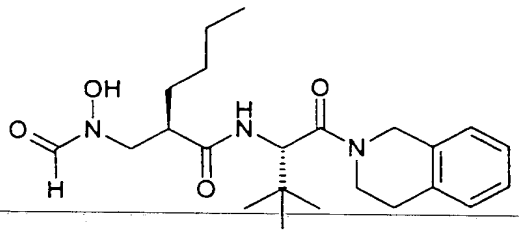
2R-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid [2,2-dimethyl-1S-(piperidine-1-carbonyl)-propyl]-amide



White foam. LRMS: +ve ion 392 [M+Na], -ve ion 368 [M-H]. HPLC: RT = 20.7min. (Purity 88%)

Example 15

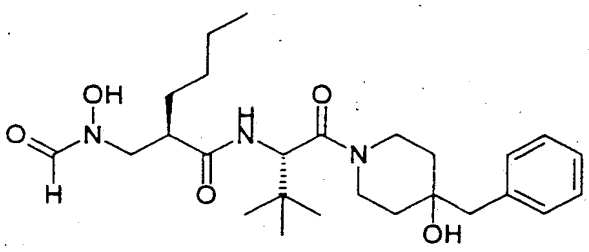
2R-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid [1S-(3,4-dihydro-1*H*-isoquinoline-2-carbonyl)-2,2-dimethyl-propyl]-amide



White foam. LRMS: +ve ion 440 [M+Na], -ve ion 416 [M-H]. HPLC: RT = 20.7min. (Purity 91%)

Example 16

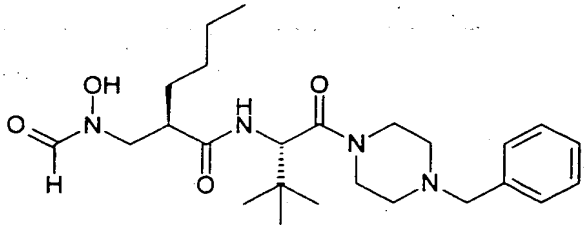
2R-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid [1S-(4-benzyl-4- hydroxy-piperidine-1-carbonyl)-2,2-dimethyl-propyl]-amide



White foam. LRMS: +ve ion 498 [M+Na], -ve ion 474 [M-H]. HPLC: RT = 21.0 min. (Purity 96%).

Example 17

2R-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid [1S-(4-benzyl-piperazine-1-carbonyl)-2,2-dimethyl-propyl]-amide

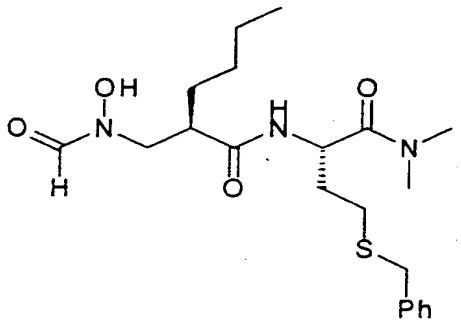


White foam. LRMS: +ve ion 461 [M+H]. HPLC: RT = 16.6min. (Purity 86%).

The compounds of Examples 18 to 25 were prepared by analogy with the method described in Example 2.

Example 18

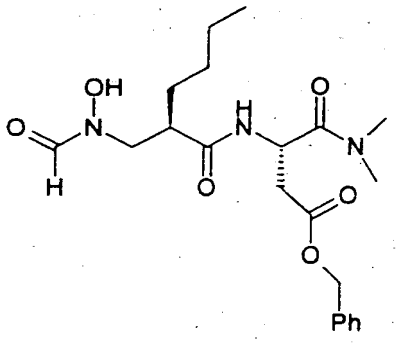
2R-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid (3-benzylsulfanyl-1S-dimethylcarbamoyl-propyl)-amide



Pale yellow gum. ^{1}H-NMR; δ ($CDCl_3$, rotamers), 8.39 (0.4H, s), 7.80 (0.6H, s), 7.27 (5H, m), 7.10 (0.4H, d, J = 7.9 Hz), 6.97 (0.6H, d, J = 8.3 Hz), 5.04 (1H, m), 4.03 (0.4H, dd, J = 14.6 & 7.6 Hz), 3.73 (2.6H, m), 3.47 (1H, m), 3.06 (1.2H, s), 3.03 (1.8H, s), 2.94 (1.2H, s), 2.92 (1.8H, s), 2.78 (0.6H, m), 2.62 (0.4H, m), 2.40 (2H, m), 1.54 (8H, m) and 0.86 (3H, t, J = 6.6 Hz). ^{13}C-NMR; δ (CD_3OD, rotamers), 176.5, 176.2, 173.8, 173.7, 140.4, 130.4, 129.9, 128.5, 128.4, 53.9, 50.7, 49.9, 45.9, 45.8, 38.1, 37.3, 36.6, 32.8, 32.1, 31.4, 31.3, 30.7, 28.9, 28.8, 28.6, 24.1 and 14.7. LRMS: +ve ion 424 [M+H], 446 [M+Na].

Example 19

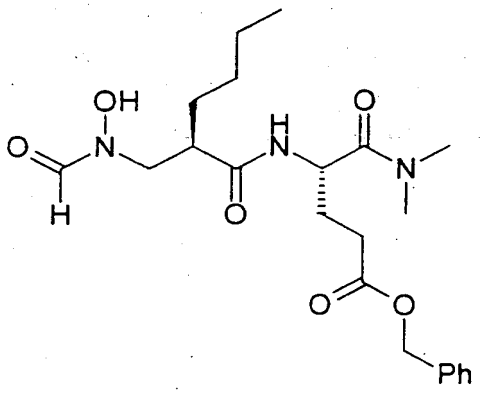
3S-{2R-[(Formyl-hydroxy-amino)-methyl]-hexanoylamino}-*N*,*N*-dimethyl-succinamic acid benzyl ester



White solid. ^{1}H-NMR; δ ($CDCl_3$, rotamers), 8.36 (0.3H, s), 7.79 (0.7H, s), 7.23 (6H, m), 5.30 (1H, m), 5.09 (2H, m), 3.96 (0.3H, dd, J = 14.2 & 8.6 Hz), 3.71 (0.7H, dd, J = 13.9 & 10.1 Hz), 3.47 (1H, m), 3.09 (1H, s), 3.06 (2H, s), 2.92 (1H, s), 2.91 (2H, s), 2.82 (3H, m), 1.68 (1H, m), 1.33 (5H, m) and 0.86 (3H, m). ^{13}C-NMR; δ ($CDCl_3$, rotamers), 175.0, 173.1, 171.0, 170.7, 135.9, 129.0, 128.9, 128.8, 67.6, 67.3, 52.5, 49.2, 46.7, 46.4, 46.1, 45.9, 45.1, 37.7, 37.5, 37.4, 36.5, 36.4, 30.0, 29.8, 22.9 and 14.3. LRMS: +ve ion 444 [M+Na], 422 [M+H].

Example 20

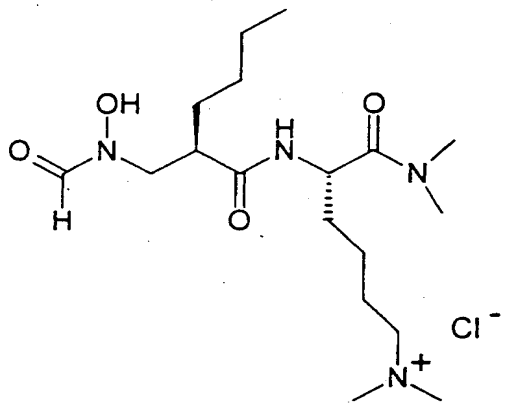
4S-Dimethylcarbamoyl-4-{2R-[(formyl-hydroxy-amino)-methyl]-hexanoylamino }-butyric acid benzyl ester



Pale yellow oil. LRMS: +ve ion 458 [M+Na], -ve ion 434 [M-H].

Exampl 21

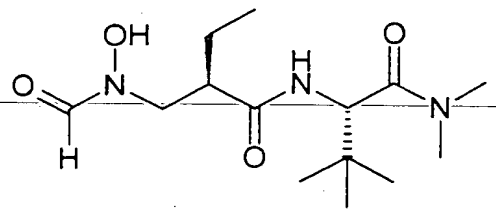
(5S-Dimethylcarbamoyl-5-{2R-[(formyl-hydroxy-amino)-methyl]-hexanoylamino}-pentyl)-dimethyl-ammonium chloride



Yellow oil. ^{1}H-NMR; δ ($CDCl_3$), 7.77 (1H, s), 7.45 (1H, d, J = 8.9 Hz), 4.99 (1H, m), 3.81 (1H, m), 3.46 1H, m), 3.09 (6H, s), 2.98 (3H, m), 2.97 (3H, s), 2.95 (3H, s), 1.51 (12H, m) and 0.88 (3H, m). ^{13}C-NMR; δ ($CDCl_3$), 173.6, 171.5, 158.8, 58.2, 53.6, 48.6, 45.4, 37.6, 36.2, 31.4, 30.2, 29.7, 24.7, 23.0, 22.5 and 14.3. LRMS: +ve ion 373 [M+H].

Example 22

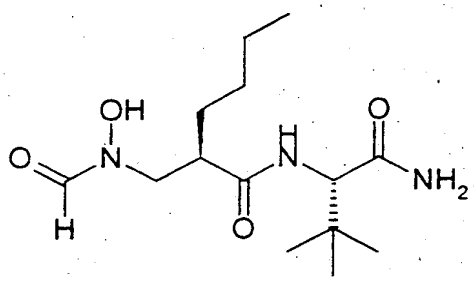
2R-[(Formyl-hydroxy-amino)-methyl]-butyric acid (1S-carbamoyl-2,2-dimethyl-propyl) amide.



White hygroscopic solid. ^{1}H-NMR; δ ($CDCl_3$), 9.29 (0.4H, s), 8.41 (0.4H, s), 7.84 (0.6H, s), 6.67 (0.4H, d, J = 6.7 Hz), 6.52 (0.6H, d, J = 10.1 Hz), 4.92-4.85 (1H, m), 4.05 (0.4H, dd, J = 14.6 & 6.6 Hz), 3.84 (0.6H, dd, J = 13.9 & 9.6 Hz), 3.59 (0.4H, dd, J = 14.7 & 3.3 Hz), 3.50 (0.6H, dd, J = 5.5 & 4.2 Hz), 3.16 (1.2H, s), 3.15 (1.8H, s), 2.98 (1.2H, s), 2.96 (1.8H, s), 2.72 (0.4H, m), 2.58 (0.6H, m), 1.68-1.42 (2H, m), 1.00-0.96 (9H, m) and 0.92-0.89 (3H, m).
^{13}C-NMR; δ ($CDCl_3$), 173.1, 55.5, 54.9, 51.7, 48.4, 48.0, 46.6, 38.9, 38.8, 36.3, 36.1, 31.3, 27.0, 26.9, 23.9, 23.8 and 12.1. LRMS: +ve ion 324 [M+Na] 300 [M-H].

Example 23

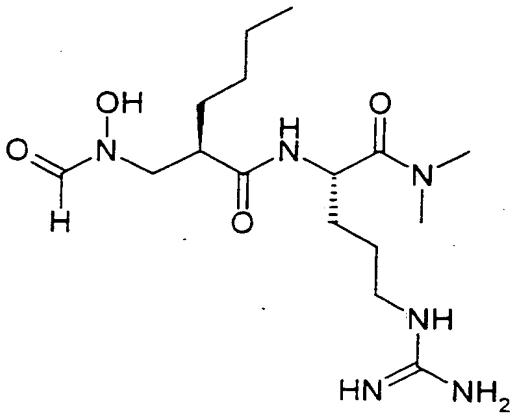
2R-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid (1S-carbamoyl-2,2-dimethyl-propyl) amide.



White powder. ^{1}H-NMR; δ($(CD_3)_2SO$), 9.95 (0.4H, s), 9.50 (0.6H, s), 8.24 (0.4H, s), 7.79 (0.6H, s), 7.74 (1H, br m), 7.42 (1H, br s), 7.04 (1H, br s), 4.22 (1H, d, J = 9.5 Hz), 3.69-3.26 (2H, m), 2.98-2.75 (1H, br m), 1.55-1.02 (6H, br m), 0.91 (9H, s) and 0.84 (3H, t, J = 6.8 Hz). ^{13}C-NMR; δ($(CD_3)_2SO$), 172.9, 172.4, 79.5, 60.0, 52.3, 48.7, 43.4, 43.2, 34.1, 29.8, 28.9, 27.1, 22.5 and 14.2. LRMS: +ve ion 324 [M+Na], 302 [M+H]. –ve ion 300 [M-H].

Example 24

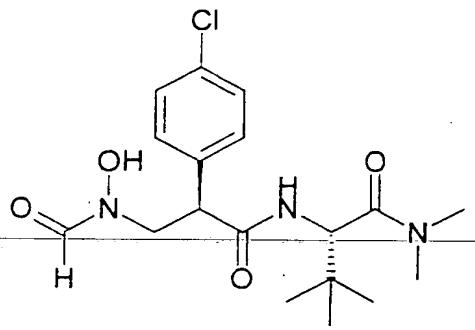
2R-[Formyl-hydroxy-amino)-methyl]-hexanoic acid (1S-dimethyl-carbamoyl-4-guanidinobutyl)-amide



White powder. ^{1}H-NMR; δ(CD_3OD, rotamers), 8.12 (0.1H, s), 7.60 (0.9H, s), 4.90 (1H, m), 3.67 (1H, dd, J =12.2, 12.2 Hz), 3.38 (1H, m), 3.22-3.09 (2H, m), 3.11 (3H, s), 3.02 (1H, m), 2.94 (3H, s), 1.74-1.47 (5H, m), 1.47-1.20 (5H, m) and 0.90 (3H, t, J = 6.6 Hz). ^{13}C-NMR; δ(CD_3OD, rotamers), 174.4, 172.0, 157.9, 55.9, 49.0, 45.0, 41.4, 37.7, 36.2, 30.6, 29.8, 29.7, 25.1, 23.2 and 14.4.
LRMS: +ve ion 373 [M+H].

Example 25

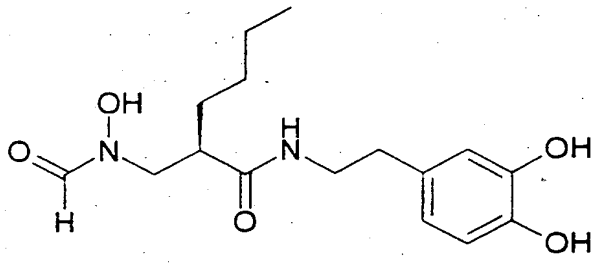
[2R-(4-chlorophenyl)-3-(formyl-hydroxy-amino)-propionylamino]-2S-3,3,*N,N*-tetramethyl-butyramide



Colourless oil. ^{1}H-NMR: δ($CDCl_3$, rotamers), 8.35 (0.25H, s), 7.78 (0.75H, s), 7.29 (4H, s), 7.08 (1H, d, J = 9.4 Hz), 4.89 (1H, d, J = 9.3 Hz), 4.28-4.07 (2H, m), 3.84 (0.25H, dd, J = 13.3 & 3.5 Hz), 3.63 (0.75H, dd, J = 13.1 & 4.4 Hz), 3.10 (1H, s), 3.07 (2H, s), 2.91 (1H, s), 2.88 (2H, s), 0.92 (9H, s); LRMS: +ve ion 384 [M+H].

Example 26

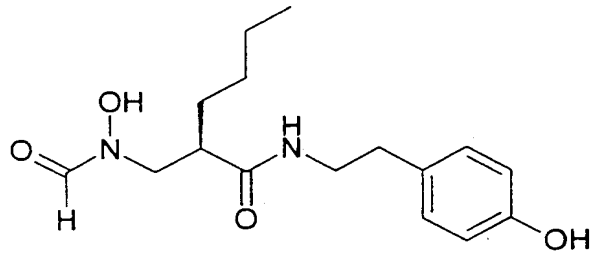
2R-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid [2(3,4-dihydroxy-phenyl)-ethyl]-amide



Yellow solid. ^{1}H-NMR: δ(CD_3OD, rotamers), 8.25 (0.3H, s), 8.08 (1H, m), 7.85 (0.7H, s), 6.68 (2H, m), 6.51 (1H, m), 3.70 (1H, m), 3.35 (3H, m), 2.80-2.50 (3H, m), 1.60-1.10 (6H, m) and 0.89 (3H, t, J = 6.6 Hz); ^{13}C-NMR: δ(CD_3OD, rotamers), 176.5, 176.1, 146.7, 145.2, 132.3, 121.5, 117.8, 116.8, 60.7, 46.2, 46.1, 42.6, 36.3, 31.3, 30.8, 24.1 and 14.7; LRMS: +ve ion 325 [M+H], 347 [M+Na]; -ve ion 323 [M-H].

Example 27

2R-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid [2(4-hydroxy-phenyl)-ethyl]-amide



White solid. ^{1}H-NMR: δ(CD_3OD, rotamers), 8.24 (0.3H, s), 8.10 (1H, br m), 7.84 (0.7H, s), 7.03 (2H, d, J = 8 Hz), 6.70 (2H, d, J = 7 Hz), 3.68 (1H, m), 3.35 (3H, m), 2.70 (3H, m), 1.65-1.10 (6H, m) and 0.90 (3H, t, J = 7.0 Hz); ^{13}C-NMR: δ(CD_3OD, rotamers), 176.5, 176.1, 157.3, 131.6, 131.2, 116.7, 53.9, 46.1, 45.1, 42.9, 36.1, 31.7, 31.2, 24.1 and 14.7.; LRMS: +ve ion 309 [M+H], 331 [M+Na]; -ve ion 307 [M-H].

Biological Example A

Demonstration of antibacterial effect

a).

Minimal inhibitory concentrations (MIC) of inhibitors against *E. coli* strain DH5α (Genotype; F-φ80d*lac*ZΔM15Δ(*lac*ZYA-*arg*F)U169 *deo*R *rec*A1 *end*A1 *hsd*R17(r_k^-,m_k^+)*pho*A *sup*E44λ$^-$ *thi*-1 *gyr*A96 *rel*A1) obtained from GibcoBRL Life Technologies, *Enterobacter cloacae* (American Type Culture Collection number 13047), *Klebsiella pneumoniae* (American Type Culture Collection number 13883) or *Staphylococcus capitis* (American Type Culture Collection number 35661) were determined as follows. Stock solutions of test compound (Compounds 1 and 2 from Examples 1 and 2 respectively (both isomer A)) and three standard laboratory antibiotics, carbenicillin (Sigma, catalogue No. C3416), kanamycin (Sigma, catalogue No. K4000) and chloramphenicol (Sigma, catalogue No. C1919), were prepared by dissolution of each compound in dimethylsulfoxide at 10mM. For the determination of the minimal inhibitory concentration, two fold serial dilutions were prepared in 2xYT broth (typtone 16g/1, yeast extract 10g/1, sodium chloride 5g/1 obtained from BIO 101 Inc, 1070 Joshua Way, Vista, CA92083, USA) to yield 0.05 ml compound-containing medium per well. Inocula were prepared from cultures grown overnight in 2xYT broth at 37°C. Cell densities were adjusted to absorbance at 660nm (A_{660}) = 0.1; the optical density-standardised preparations were diluted 1:1000 in 2xYT broth; and each well inoculated with 0.05ml of the diluted bacteria. Microtitre plates were incubated at 37°C for 18 hours in a humidified incubator. The MIC (μM) was recorded as the lowest drug concentration that inhibited visible growth. The compounds of the Examples inhibited bacterial growth. For example,

the compound of Example 7 had an MIC against E. coli of 12.5 μM.

Biological Example B

i) *Cloning of the Escherichia coli PDF gene.*

The *E. coli* PDF gene was cloned in pET24a(+) (designated pET24-PDF) and was used to transform BL21 DE3 cells from Novagen Inc, (Madison, Wisconsin). Clones were selected at 37°C on YT agar plates (8g/l typtone, 5g/yeast extract, NaCl 5g/l, agar 15g/l) supplemented with 30μg/ml kanamycin.

ii) *Expression of PDF*

A 20ml overnight culture of BL21 DE3 cells harbouring pET24-PDF was used to infect 500ml 2xYT broth (16g/l typtone, 10g/l yeast extract, NaCl 5g/l) containing 30ug/ml kanamycin in a 2 litre baffled flask and grown at 37°C with shaking to an OD_{600} 0.6. The culture was then induced by adjusting the medium to 1.0mM isopropyl β-D thiogalactopyranoside (IPTG). The induction was allowed to proceed for a further 3 hours at 37°C, the cells were harvested by centrifugation and the cell pellet washed with 250ml phosphate buffered saline (PBS) and the pellet stored at -70°C.

iii) *Preparation of soluble protein fraction.*

The cells from a 1 litre expression were resuspeneded in 2x 25ml of ice cold phosphate buffered saline. The cell suspension was sonicated on ice using an MSE Soniprep 150 fitted with a medium probe and at an amplitude of 20-25 microns in 6x20 second pluses. The resulting suspension was then cleared by centrifugation at 20,000 xg for 15 minutes. The supernatant was then used for further purification of the enzyme.

iv) *PDF Purification*

E. coli lysate from a 1l culture in phosphate buffered saline (PBS) were adjusted to 2M ammonium sulphate. A 15ml phenyl sepharose column was equilibrated with PBS/2M ammonium sulphate at 4°C. The lysate was loaded on the column and washed with equilibration buffer. The column was eluted by reducing the ammonium sulphate concentration from 2M to 0M over 10 column volumes. 5ml fractions were collected and analysed by SDS-PAGE. The fractions containing the majority of the 20kDa PDF were pooled. The pooled fractions were concentrated using a 3kDa cutoff membrane to a volume of 5ml. The fraction was then loaded onto a Superdex 75 (size exclusion chromatography) column equilibrated in PBS. The concentrated PDF pool eluted at one ml/min at 4°C and 5ml fractions collected and analysed by SDS-PAGE. The purest fractions were pooled and stored at -70°C.

(v) *PDF in vitro assay*

The assay was performed in a single 96 well plate in a final volume of 100µl containing:

- 20µl PDF (4µg/ml)
- 20µl 100mM Hepes pH 7.0 + 1M KCl + 0.05% Brij
- 10µl serial dilution of test compound in 20% DMSO
- 50µl formyl-Met-Ala-Ser (8mM)

The assay was incubated at 37°C for 30 minutes. The free amino group of the deformylated (Met-Ala-Ser) product was detected using fluorescamine, by the following additions:

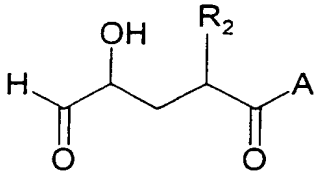
- 50µl 0.2M borate pH 9.5
- 50µl fluorescamine (150µg/ml in dry dioxane)

Fluorescence was quantified on SLT Fluostar plate reader using an excitation wavelength of 390nM and an emission wavelength of 485nM. Standard control reactions are a no inhibitor reaction which provides the zero inhibition figure and a no enzyme and no inhibitor reaction which provides the 100% inhibition figure. The data was analysed by conversion of the fluorescence units to % inhibition and the inhibitor concentration plotted against % inhibition. The data was fitted to a sigmoidal function : $y = A+((B-A)/(1+((C/x)^D)))$, wherein A represents zero inhibition, B represents 100% inhibition and C represents the IC_{50}, D represents the slope. The IC_{50} represents the concentration of inhibitor (nM) required to decrease enzyme activity by 50%.

The compounds of the invention were found to inhibit bacterial PDF *in vitro.*

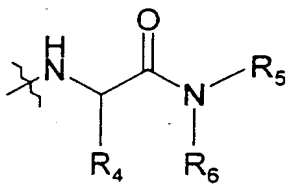
Claims :

1. A compound of formula (I) or a pharmaceutically or veterinarily acceptable salt hydrate or solvate thereof



(I)

wherein R_2 represents a substituted or unsubstituted C_1-C_6 alkyl, cycloalkyl(C_1-C_6 alkyl)-, or aryl(C_1-C_6 alkyl)- group, and A represents a group of formula (IA), or (IB):



(IA)

(IB)

wherein R_4 represents the side chain of a natural or non-natural alpha amino acid, and R_5 and R_6 are each independently hydrogen or C_1-C_6 alkyl, heterocyclic or aryl(C_1-C_6 alkyl)-, or R_5 and R_6 when taken together with the nitrogen atom to which they are attached form an optionally substituted saturated heterocyclic ring of 3 to 8 atoms which ring is optionally fused to a carbocyclic or second heterocyclic ring,

characterised in that the said compound is selected from the group consisting of

N-[3S-(4-benzylpiperidine-1-carbonyl)-2,2-dimethyl-propyl]-3-cyclopentyl-2R-[(formyl-hydroxy-amino)-methyl]-propionamide,

N-[2R-(4-benzyl-piperidine-1-carbonyl)-hexyl]-N-hydroxy-formamide,

N-hydroxy-N-[2R-(2-methyl-piperidine-1-carbonyl)-hexyl]-formamide,

N-hydroxy-N-[2R-(piperidine-1-carbonyl)-hexyl]-formamide,

N-hydroxy-N-[2R-(piperazine-1-carbonyl)-hexyl]-formamide,

2R-[(formyl-hydroxy-amino)-methyl]-hexanoic acid pyrrolidin-1-ylamide,

2R-[(formyl-hydroxy-amino)-methyl]-hexanoic acid methyl-(1-methyl-piperidin-4-yl)-amide,

N-[2R-(azepane-1-carbonyl)-hexyl]-N-hydroxy-formamide,

2R-[(formyl-hydroxy-amino)-methyl]-hexanoic acid (4-methyl-piperazin-1-yl)-amide,

2R-[(formyl-hydroxy-amino)-methy]-hexanoic acid diisopropylamide,

1-{2R-[(formyl-hydroxy-amino)-methyl]-hexanoyl}-piperidine-3-carboxylic acid ethyl ester,

4-{2R-[(formyl-hydroxy-amino)-methyl]-hexanoyl}-piperazine-1-carboxylic acid ethyl ester,

4-{2R-[(formyl-hydroxy-amino)-methyl]-hexanoyl}-1,1-dimethyl-piperazinium iodide,

2R-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid [2,2-dimethyl-1S-(piperidine-1-carbonyl)-propyl]-amide,

2R-[(formyl-hydroxy-amino)-methyl]-hexanoic acid [1S-(3,4-dihydro-1*H*-isoquinoline-2-carbonyl)-2,2-dimethyl-propyl]-amide,

2R-[(formyl-hydroxy-amino)-methyl]-hexanoic acid [1S-(4-benzyl-4- hydroxy-piperidine-1-carbonyl)-2,2-dimethyl-propyl]-amide,

2R-[(formyl-hydroxy-amino)-methyl]-hexanoic acid [1S-(4-benzyl-piperazine-1-carbonyl)-2,2-dimethyl-propyl]-amide,

2R-[(formyl-hydroxy-amino)-methyl]-hexanoic acid (3-benzylsulfanyl-1S-dimethylcarbamoyl-propyl)-amide,

3S-{2R-[(formyl-hydroxy-amino)-methyl]-hexanoylamino}-*N*,*N*-dimethyl-succinamic acid benzyl ester,

4S-dimethylcarbamoyl-4-{2R-[(formyl-hydroxy-amino)-methyl]-hexanoyl-amino}-butyric acid benzyl ester,

(5S-dimethylcarbamoyl-5-{2R-[(formyl-hydroxy-amino)-methyl]-hexanoyl-amino}-pentyl)-dimethyl-ammonium chloride,

2R-[(formyl-hydroxy-amino)-methyl]-butyric acid (1-carbamoyl-2,2-dimethyl-propyl) amide,

2-[(formyl-hydroxy-amino)-methyl]-hexanoic acid (1-carbamoyl-2,2-dimethyl-propyl) amide,

2R-[formyl-hydroxy-amino)-methyl]-hexanoic acid (1-dimethyl-carbamoyl-4-guanidinobutyl)-amide,

2R-[2-(4-chlorophenyl)-3-(formyl-hydroxy-amino)-propionylamino]-2S-3,3,*N*,*N*-tetramethyl-butyramide,

2R-[(formyl-hydroxy-amino)-methyl]-hexanoic acid [2(3,4-dihydroxy-phenyl)-ethyl]-amide,

2R-[(formyl-hydroxy-amino)-methyl]-hexanoic acid [2(4-hydroxyphenyl)-ethyl]-amide,

and pharmacetically and veterinarily acceptable salts, hydrates and solvates thereof.

2. The use of a compound as claimed in claim 1 in the preparation of an antibacterial composition;

3. A method for the treatment of bacterial infections in humans and non-human mammals, which comprises administering to a subject suffering such infection an antibacterially effective dose of a compound as claimed in claim 1.

4. A method for the treatment of bacterial contamination by applying an antibacterially effective amount of a as claimed in claim 1 to the site of contamination;

5. A pharmaceutical or veterinary composition comprising a compound as claimed in claim 1 together with a pharmaceutically or veterinaril acceptable carrier.

INTERNATIONAL SEARCH REPORT

Interna[redacted]al Application No
[redacted]/GB 99/02629

A. CLASSIFICATION OF SUBJECT MA[redacted]

IPC 7 C07D211/16 C07D295/18 A61K31/16 C07D295/22 C07C259/06
C07D211/60 C07D295/20 C07D217/06 C07D211/48 C07C321/16
C07C279/14 A61K31/445 A61K31/495 A61K31/47 A61P31/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 94 10990 A (GALLOWAY WILLIAM ALAN ;BRITISH BIO TECHNOLOGY (GB); CRIMMIN MICHAE) 26 May 1994 (1994-05-26) page 14, line 8	1-5
A	FOURNIE-ZALUSKI M -C ET AL: "NEW BIDENTASES AS FULL INHIBITORS OF ENKEPHALIN-DEGRADING ENZYMES: SYNTHESIS AND ANALGESIS PROPERTIES" JOURNAL OF MEDICINAL CHEMISTRY,US,AMERICAN CHEMICAL SOCIETY. WASHINGTON, vol. 28, no. 9, 1 January 1985 (1985-01-01), pages 1158-1169, XP002019770 ISSN: 0022-2623	

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 March 2000	15/03/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax (+31–70) 340–3016	De Jong, B

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Intern. ...al Application No
...T/GB 99/02629

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D211/58

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Y JIN ET AL: "Inhibition stereochemistry of hydroxamate inhibitors for thermolysin" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS,GB,OXFORD, vol. 8, no. 24, 1998, pages 3515-3518-3518, XP002106374 ISSN: 0960-894X	
E	WO 99 39704 A (BRITISH BIOTECH PHARM ;DAVIES STEPHEN JOHN (GB); HUNTER MICHAEL GE) 12 August 1999 (1999-08-12) cited in the application the whole document	1-5

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 March 2000	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	De Jong, B

2

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

[redacted]ational application No.
PCT/GB 99/02629

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 3,4
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 3,4 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interna... al Application No
T/GB 99/02629

Patent document cited in search report	Publication date	Patent family member( )	Publication date
WO 9410990 A	26-05-1994	AT 150300 T	15-04-1997
		AU 5430194 A	08-06-1994
		DE 69309094 D	24-04-1997
		DE 69309094 T	31-07-1997
		EP 0667770 A	23-08-1995
		ES 2101358 T	01-07-1997
		JP 8505605 T	18-06-1996
		US 5691382 A	25-11-1997
WO 9939704 A	12-08-1999	AU 2529299 A	23-08-1999

PCT

Request

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only
International Application No.
International Filing Date
Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference: 205/AJW

Box No. I TITLE OF INVENTION Antibacterial Agents

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This person is applicant for the purposes of: ☐ All designated states ☐ All designated except the United States of America ☒ The United States of America only ☐ The States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on a continuation sheet

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☐ agent ☐ common representative

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Alan J. Walls British Biotech Pharmaceuticals Limited Watlington Road Cowley Oxford OX4 5LY United Kingdom	Telephone No 01865 748747 Facsimile No. 01865 781047 Teleprinter No. 838083

☐ Mark this check box where no agent or common representative is/has been appointed and the space is used instead to indicate a special address to which correspondence should be sent.

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- ☐ All designated except the United States of America
- ☒ The United States of America only
- ☐ The States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on another continuation sheet

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- [x] applicant and inventor
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- [ ] inventor only

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- [ ] All designated except the United States of America
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- [ ] inventor only

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State of residence: GB

This person is applicant for the purposes of:
- [ ] All designated states
- [ ] All designated except the United States of America
- [x] The United States of America only
- [ ] The States indicated in the Supplemental Box

Box No. V DESIGNATION OF STATES

The following designations are hereby made under rule 4.9(a)
Regional Patent

☒ **EP** European Patent: **AT** Austria, **BE** Belgium, **CH** and **LI** Switzerland and Liechtenstein, **CY** Cyprus, **DE** Germany, **DK** Denmark, **ES** Spain, **FI** Finland, **FR** France, **GB** United Kingdom, **GR** Greece, **IE** Ireland, **IT** Italy, **LU** Luxembourg, **MC** Monaco, **NL** Netherlands, **PT** Portugal, **SE** Sweden and any other state which is a Contracting State of the European Patent Convention and of the PCT

National Patent

☒ **AU** Australia

☒ **BR** Brazil

☒ **CA** Canada

☒ **CN** China

☒ **CZ** Czech Republic

☐ **DE** Germany

☒ **GB** United Kingdom

☐ **GE** Georgia

☒ **HU** Hungary

☒ **IL** Israel

☒ **JP** Japan

☒ **KR** Republic of Korea

☒ **MX** Mexico

☒ **NO** Norway

☒ **NZ** New Zealand

☒ **PL** Poland

☒ **RU** Russian Federation

☒ **SG** Singapore

☒ **SK** Slovakia

☒ **TR** Turkey

☒ **UA** Ukraine

☒ **US** United States of America

☒ **ZA** South Africa

In addition to the designations made above, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except the designation(s) of

The application declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.

Box No. VI PRIORITY CLAIM Further priority claims are indicated in the Supplemental Box ☐

The priority of the following application(s) is claimed

Country *(in which, or for which, the application was filed)*	Filing Date *(day/month/year)*	Application No.	Office of Filing (only for regional or international applications)

The receiving Office is hereby requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above at item(s):

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) (If two or more International Searching Authorities are competent to carry out the international search, indicate the authority chosen; the two-letter code may be used): **ISA/**

Earlier Search Fill in where a search (international, international type or other) by the International Searching Authority has already been carried out or requested and the Authority is now requested to base the International Search, to the extent possible, on the results of that earlier search. Identify such search search or request either by reference to the relevant application (or the translation thereof) or by reference to the search request:

Country (or regional Office):	Date (day/month/year)	Number:

Box No. VIII CHECK LIST

This international application contains the following number of sheets:

1. request	6	**sheets**
2. description	40	**sheets**
3. claims	4	**sheets**
4. abstract	1	**sheets**
5. drawings	0	**sheets**
Total	51	**sheets**

This international application is accompanied by the item(s) marked below:

- ☐ separate signed power of attorney
- ☐ copy of general power of attorney
- ☒ statement explaining lack of signature
- ☐ priority document(s) identified in Box No. VI *as item(s)*
- ☒ fee calculation sheet
- ☐ separate indications concerning deposited microorganisms
- ☐ Nucleotide and/or amino acid sequence listing
- ☐ other *(specify)*

Figure No. ☐ of the drawings (if any) should accompany the abstract when it is published.

Box No. IX SIGNATURE OF APPLICANT OR AGENT (see supplemtary Box IX)

Alan Hastings Drummond, Director
For and on behalf of
British Biotech Pharmaceuticals Ltd

Michael George HUNTER

Raymond Paul BECKETT

John Martin CLEMENTS

Mark WHITTAKER

Stephen John DAVIES

For receiving Office use only

1. Date of actual receipt of the purported International application:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:
4. Date of timely receipt of the required corrections under PCT Article 11(2):
5. International Searching Authority specified by the applicant:

2. Drawings
☐ received
☐ not received

ISA/

6. ☐ Transmittal of search copy delayed until search fee is paid

For International Bureau use only

Date of receipt of the record copy by the international Bureau

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

WALLS, Alan J.
British Biotech Pharmaceuticals Ltd
Watlington Road
Cowley
Oxford OX4 5LY
GRANDE BRETAGNE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	
Applicant's or agent's file reference 205/AJW	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB99/02629	10/08/1999	10/08/1999

Applicant
BRITISH BIOTECH PHARMACEUTICALS LTD et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Ambroa, J.R. Tel.+49 89 2399-8012

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
205/AJW		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB99/02629	10/08/1999	10/08/1999
International Patent Classification (IPC) or national classification and IPC C07D211/16		
Applicant BRITISH BIOTECH PHARMACEUTICALS LTD et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 7 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
03/03/2000	
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Mathys, E Telephone No. +49 89 2399 8596

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB99/02629

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-40	as originally filed				

Claims, No.:

1-4	as received on	22/07/2000	with letter of	19/07/2000	

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   ☐ the language of publication of the international application (under Rule 48.3(b)).
   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.
   ☐ filed together with the international application in computer readable form.
   ☐ furnished subsequently to this Authority in written form.
   ☐ furnished subsequently to this Authority in computer readable form.
   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:
   ☐ the claims, Nos.:
   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims 1-4
	No:	Claims
Inventive step (IS)	Yes:	Claims 1-4
	No:	Claims
Industrial applicability (IA)	Yes:	Claims 1-4
	No:	Claims

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

ITEM V

Novelty

(D1) WO-A-94/10990, (D2) JOURNAL OF MEDICINAL CHEMISTRY, vol. 28, no. 9, 1985, pages 1158-1169 and (D3) BIOORGANIC & MEDICINAL CHEMISTRY and (D4)WO-A-99/39704 do not disclose specifically a compounds listed in present claims 1 and 4.

Inventive Step

The compounds listed in claim 1 represent partly a selection from the general formula (Ib) disclosed by (D1) WO-A-94/10990, which represents the closest state of the art. D1 discloses the usefulness of the compounds to counteract the effects of TNT from cells (see e.g. claim 21), but not their direct usefulness in combatting bacterial infections. This usefulness is neither suggested by D2 to D4.
The specific compounds according to claim 4 are not disclosed by any of the documents D1 to D4 nor do they represent a selection out of general formulae disclosed there.

Industrial Applicability

For the assessment of present claims 2 and 3 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

ITEM VI

WO-A-99/39704

ITEM VII

The description is not in conformity with the claims and does not mention the relevant background represented by the above cited documents as required by Rule 5.1(a)(ii) and (iii) PCT.

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:
WALLS, Alan, J.
British Biotech Pharmaceuticals Limited
Watlington Road
Cowley
Oxford OX4 5LY
ROYAUME-UNI

Date of mailing (day/month/year) 15 February 2001 (15.02.01)	
Applicant's or agent's file reference 205/AJW	**IMPORTANT NOTICE**

International application No.	**International filing date** (day/month/year)	**Priority date** (day/month/year)
PCT/GB99/02629	10 August 1999 (10.08.99)	

Applicant
BRITISH BIOTECH PHARMACEUTICALS LIMITED et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
   AU,KR,US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   BR,CA,CN,CZ,EP,GB,HU,IL,JP,MX,NO,NZ,PL,RU,SG,SK,TR,UA,ZA

   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
   15 February 2001 (15.02.01) under No. WO 01/10835

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, **a demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer
J. Zahra

Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

INFORMATION CONCERNING ELECTED OFFICES NOTIFIED OF THEIR ELECTION

(PCT Rule 61.3)

To:
WALLS, Alan, J.
British Biotech Pharmaceuticals Limited
Watlington Road
Cowley
Oxford OX4 5LY
ROYAUME-UNI

Date of mailing (day/month/year)
15 February 2001 (15.02.01)

Applicant's or agent's file reference
205/AJW

IMPORTANT INFORMATION

International application No.	**International filing date** (day/month/year)	**Priority date** (day/month/year)
PCT/GB99/02629	10 August 1999 (10.08.99)	

Applicant
BRITISH BIOTECH PHARMACEUTICALS LIMITED et al

1. The applicant is hereby informed that the International Bureau has, according to Article 31(7), notified each of the following Offices of its election:

   EP :AT,BE,CH,CY,DE,DK,ES,FI,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE
   National :AU,CA,CN,CZ,IL,JP,KR,NO,NZ,PL,RU,SK,US

2. The following Offices have waived the requirement for the notification of their election; the notification will be sent to them by the International Bureau only upon their request:

   National :BR,GB,HU,MX,SG,TR,UA,ZA

3. The applicant is reminded that he must enter the "national phase" **before the expiration of 30 months from the priority date** before each of the Offices listed above. This must be done by paying the national fee(s) and furnishing , if prescribed, a translation of the international application (Article 39(1)(a)), as well as, where applicable, by furnishing a translation of any annexes of the international preliminary examination report (Article 36(3)(b) and Rule 74.1).

   Some offices have fixed time limits expiring later than the above-mentioned time limit. For detailed information about the applicable time limits and the acts to be performed upon entry into the national phase before a particular Office, see Volume II of the PCT Applicant's Guide.

   The entry into the European regional phase is postponed **until 31 months from the priority date** for all States designated for the purposes of obtaining a European patent.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer:
J. Zahra

Telephone No. (41-22) 338.83.38

ADSOT

13

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
205/AJW		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB99/02629	10/08/1999	10/08/1999

International Patent Classification (IPC) or national classification and IPC
C07D211/16

Applicant
BRITISH BIOTECH PHARMACEUTICALS LTD et al.

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 7 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
03/03/2000	

Name and mailing address of the international preliminary examining authority:
European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer
Mathys, E

Telephone No. +49 89 2399 8596

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB99/02629

I. Basis f the r port

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-40 as originally filed

Claims, No.:

1-4 as received on 22/07/2000 with letter of 19/07/2000

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequenc listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims 1-4
	No:	Claims
Inventive step (IS)	Yes:	Claims 1-4
	No:	Claims
Industrial applicability (IA)	Yes:	Claims 1-4
	No:	Claims

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
s e separate sheet

ITEM V

Novelty

(D1) WO-A-94/10990, (D2) JOURNAL OF MEDICINAL CHEMISTRY, vol. 28, no. 9, 1985, pages 1158-1169 and (D3) BIOORGANIC & MEDICINAL CHEMISTRY and (D4)WO-A-99/39704 do not disclose specifically a compounds listed in present claims 1 and 4.

Inventive Step

The compounds listed in claim 1 represent partly a selection from the general formula (Ib) disclosed by (D1) WO-A-94/10990, which represents the closest state of the art. D1 discloses the usefulness of the compounds to counteract the effects of TNT from cells (see e.g. claim 21), but not their direct usefulness in combatting bacterial infections. This usefulness is neither suggested by D2 to D4.
The specific compounds according to claim 4 are not disclosed by any of the documents D1 to D4 nor do they represent a selection out of general formulae disclosed there.

Industrial Applicability

For the assessment of present claims 2 and 3 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

ITEM VI

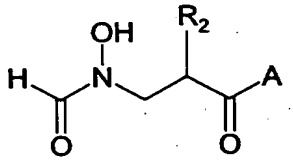
WO-A-99/39704

ITEM VII

The description is not in conformity with the claims and does not mention the relevant background represented by the above cited documents as required by Rule 5.1(a)(ii) and (iii) PCT.

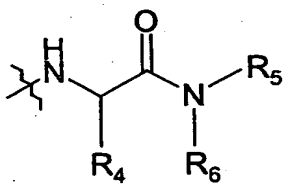
Claims :

1. The use of a compound of formula (I) or a pharmaceutically or veterinarily acceptable salt hydrate or solvate thereof in the preparation of an antibacterial composition:



(I)

wherein R_2 represents a substituted or unsubstituted C_1-C_6 alkyl, cycloalkyl(C_1-C_6 alkyl)-, or aryl(C_1-C_6 alkyl)- group, and A represents a group of formula (IA), or (IB):



(IA)

(IB)

wherein R_4 represents the side chain of a natural or non-natural alpha amino acid, and R_5 and R_6 are each independently hydrogen or C_1-C_6 alkyl, heterocyclic or aryl(C_1-C_6 alkyl)-, or R_5 and R_6 when taken together with the nitrogen atom to which they are attached form an optionally substituted saturated heterocyclic ring of 3 to 8 atoms which ring is optionally fused to a carbocyclic or second heterocyclic ring,

characterised in that the said compound is selected from the group consisting of

N-[3S-(4-benzylpiperidine-1-carbonyl)-2,2-dimethyl-propyl]-3-cyclopentyl-2R-[(formyl-hydroxy-amino)-methyl]-propionamide,

N-[2R-(4-benzyl-piperidine-1-carbonyl)-hexyl]-N-hydroxy-formamide,

N-hydroxy-N-[2R-(2-methyl-piperidine-1-carbonyl)-hexyl]-formamide,

N-hydroxy-N-[2R-(piperidine-1-carbonyl)-hexyl]-formamide,

N-hydroxy-N-[2R-(piperazine-1-carbonyl)-hexyl]-formamide,

2R-[(formyl-hydroxy-amino)-methyl]-hexanoic acid pyrrolidin-1-ylamide,

2R-[(formyl-hydroxy-amino)-methyl]-hexanoic acid methyl-(1-methyl- piperidin-4-yl)-amide,

N-[2R-(azepane-1-carbonyl)-hexyl]-N-hydroxy-formamide,

2R-[(formyl-hydroxy-amino)-methyl]-hexanoic acid (4-methyl-piperazin-1-yl)- amide,

2R-[(formyl-hydroxy-amino)-methy]-hexanoic acid diisopropylamide,

1-{2R-[(formyl-hydroxy-amino)-methyl]-hexanoyl}-piperidine-3-carboxylic acid ethyl ester,

4-{2R-[(formyl-hydroxy-amino)-methyl]-hexanoyl}-piperazine-1-carboxylic acid ethyl ester,

4-{2R-[(formyl-hydroxy-amino)-methyl]-hexanoyl}-1,1-dimethyl-piperazinium iodide,

2R-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid [2,2-dimethyl-1S-(piperidine-1-carbonyl)-propyl]-amide,

2R-[(formyl-hydroxy-amino)-methyl]-hexanoic acid [1S-(3,4-dihydro-1*H*-isoquinoline-2-carbonyl)-2,2-dimethyl-propyl]-amide,

2R-[(formyl-hydroxy-amino)-methyl]-hexanoic acid [1S-(4-benzyl-4-hydroxy- piperidine-1-carbonyl)-2,2-dimethyl-propyl]-amide,

2R-[(formyl-hydroxy-amino)-methyl]-hexanoic acid [1S-(4-benzyl-piperazine-1-carbonyl)-2,2-dimethyl-propyl]-amide,

2R-[(formyl-hydroxy-amino)-methyl]-hexanoic acid (3-benzylsulfanyl-1S- dimethylcarbamoyl-propyl)-amide,

3S-{2R-[(formyl-hydroxy-amino)-methyl]-hexanoylamino}-*N*,*N*-dimethyl-succinamic acid benzyl ester,

4S-dimethylcarbamoyl-4-{2R-[(formyl-hydroxy-amino)-methyl]-hexanoyl-amino}-butyric acid benzyl ester,

(5S-dimethylcarbamoyl-5-{2R-[(formyl-hydroxy-amino)-methyl]-hexanoyl-amino}-pentyl)-dimethyl-ammonium chloride,

2R-[(formyl-hydroxy-amino)-methyl]-butyric acid (1-carbamoyl-2,2-dimethyl-propyl) amide,

2-[(formyl-hydroxy-amino)-methyl]-hexanoic acid (1-carbamoyl-2,2-dimethyl-propyl) amide,

2R-[formyl-hydroxy-amino)-methyl]-hexanoic acid (1-dimethyl-carbamoyl-4-guanidinobutyl)-amide,

2R-[2-(4-chlorophenyl)-3-(formyl-hydroxy-amino)-propionylamino]-2S-3,3,*N*,*N*-tetramethyl-butyramide,

2R-[(formyl-hydroxy-amino)-methyl]-hexanoic acid [2(3,4-dihydroxy-phenyl)-ethyl]-amide,

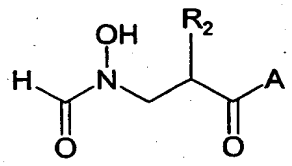
2R-[(formyl-hydroxy-amino)-methyl]-hexanoic acid [2(4-hydroxyphenyl)-ethyl]-amide,

and pharmacetically and veterinarily acceptable salts, hydrates and solvates thereof.

2. A method for the treatment of bacterial infections in humans and non-human mammals, which comprises administering to a subject suffering such infection an antibacterially effective dose of a compound as specified in claim 1.

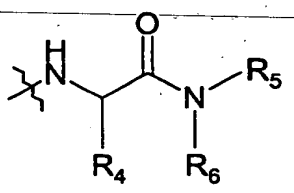
3. A method for the treatment of bacterial contamination by applying an antibacterially effective amount of a compound as specified in claim 1 to the site of contamination;

4. A compound of formula (I) or a pharmaceutically or veterinarily acceptable salt hydrate or solvate thereof



(I)

wherein R_2 represents a substituted or unsubstituted C_1-C_6 alkyl, cycloalkyl(C_1-C_6 alkyl)-, or aryl(C_1-C_6 alkyl)- group, and A represents a group of formula (IA), or (IB):



(IA)

(IB)

wherein R_4 represents the side chain of a natural or non-natural alpha amino acid, and R_5 and R_6 are each independently hydrogen or C_1-C_6 alkyl, heterocyclic or aryl(C_1-C_6 alkyl)-, or R_5 and R_6 when taken together with the nitrogen atom to which they are attached form an optionally substituted saturated heterocyclic ring of 3 to 8 atoms which ring is optionally fused to a carbocyclic or second heterocyclic ring,

characterised in that the said compound is selected from the group consisting of

N-[3S-(4-benzylpiperidine-1-carbonyl)-2,2-dimethyl-propyl]-3-cyclopentyl-2R-[(formyl-hydroxy-amino)-methyl]-propionamide,

N-[2R-(4-benzyl-piperidine-1-carbonyl)-hexyl]-N-hydroxy-formamide,

N-hydroxy-N-[2R-(2-methyl-piperidine-1-carbonyl)-hexyl]-formamide,

N-hydroxy-N-[2R-(piperidine-1-carbonyl)-hexyl]-formamide,

N-hydroxy-N-[2R-(piperazine-1-carbonyl)-hexyl]-formamide,

2R-[(formyl-hydroxy-amino)-methyl]-hexanoic acid pyrrolidin-1-ylamide,

2R-[(formyl-hydroxy-amino)-methyl]-hexanoic acid methyl-(1-methyl- piperidin-4-yl)-amide,

N-[2R-(azepane-1-carbonyl)-hexyl]-N-hydroxy-formamide,

2R-[(formyl-hydroxy-amino)-methyl]-hexanoic acid (4-methyl-piperazin-1-yl)- amide,

2R-[(formyl-hydroxy-amino)-methy]-hexanoic acid diisopropylamide,

1-{2R-[(formyl-hydroxy-amino)-methyl]-hexanoyl}-piperidine-3-carboxylic acid ethyl ester,

4-{2R-[(formyl-hydroxy-amino)-methyl]-hexanoyl}-piperazine-1-carboxylic acid ethyl ester,

4-{2R-[(formyl-hydroxy-amino)-methyl]-hexanoyl}-1,1-dimethyl-piperazinium iodide,

2R-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid [2,2-dimethyl-1S-(piperidine-1-carbonyl)-propyl]-amide,

2R-[(formyl-hydroxy-amino)-methyl]-hexanoic acid [1S-(3,4-dihydro-1*H*-isoquinoline-2-carbonyl)-2,2-dimethyl-propyl]-amide,

2R-[(formyl-hydroxy-amino)-methyl]-hexanoic acid [1S-(4-benzyl-4-hydroxy- piperidine-1-carbonyl)-2,2-dimethyl-propyl]-amide,

2R-[(formyl-hydroxy-amino)-methyl]-hexanoic acid [1S-(4-benzyl-piperazine-1-carbonyl)-2,2-dimethyl-propyl]-amide,

2-[(formyl-hydroxy-amino)-methyl]-hexanoic acid (1-carbamoyl-2,2-dimethyl-propyl) amide,

2R-[2-(4-chlorophenyl)-3-(formyl-hydroxy-amino)-propionylamino]-2S-3,3,*N*,*N*-tetramethyl-butyramide,

2R-[(formyl-hydroxy-amino)-methyl]-hexanoic acid [2(3,4-dihydroxy-phenyl)-ethyl]-amide,

2R-[(formyl-hydroxy-amino)-methyl]-hexanoic acid [2(4-hydroxyphenyl)-ethyl]-amide,

and pharmacetically and veterinarily acceptable salts, hydrates and solvates thereof.

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
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CP2/5C24
Arlington, VA 22202
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in its capacity as elected Office

Date of mailing: 15 February 2001 (15.02.01)	
International application No.: PCT/GB99/02629	Applicant's or agent's file reference: 205/AJW
International filing date: 10 August 1999 (10.08.99)	Priority date:
Applicant: HUNTER, Michael, George et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International preliminary Examining Authority on:

03 March 2000 (03.03.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
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1211 Geneva 20, Switzerland

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